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THE ADRENAL SYSTEM.

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THE INTERNAL SECRETIONS

AND THE

PRINCIPLES OF MEDICINE

BY

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VOLUME FIRST

WITH FORTY-TWO ILLUSTRATIONS

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PREFACE AND SUMMARY OF CONTENTS.

The late Professor Virchow once remarked with his characteristic frankness: "We must not deceive ourselves or one another in respect to the present condition of medical science. Unmistakably, medical men are tired of the many new hypothetical systems that are thrown aside as rubbish only to be replaced by similar ones. We shall soon see that observation and experiments alone have permanent value." Two years ago, Prof. William Osler expressed kindred views in a general summary of the progress of medicine during the nineteenth century, and radical expressions of a similar kind are not infrequently met with in current medical literature.

When, early in the year 1888, we wrote the first "Preface" of the "Annual of the Universal Medical Sciences," the purpose of the work was defined in the following words: "It is expected to become a helpmate to the practitioner in his efforts to relieve suffering, and to assist the investigator by correlating facts, thus enabling him to better compare." The successor of the "Annual," the "Analytical Cyclopædia of Practical Medicine," was framed with the same underlying thought as guide. It is not within our power to state whether these purposes have at all been attained, or whether, apart from their immediate usefulness to the practicing physician, these works have ever opened new channels of thought; we can say, however, that we have always deemed it our duty to closely follow the development of the various branches of medical science as the yearly panorama passed before our eyes, in the hope that we might eventually collate the necessary elements for a more solid foundation than Medicine now possesses. The present volume is submitted to the profession as the result of our efforts in this direction.

The pre-eminent impression which has been our beacon in the preparation of this work differs somewhat from the interpretation of the status of medical science published by the distinguished authors mentioned, in that we have been led to

regard the majority of hypothetical conceptions now interspersed throughout the many subdivisions of medical science as temporary, though artificial, factors. Our knowledge of a given disease, for example, might, as viewed from our standpoint, be compared to a chain in which the majority of links are of gold and the rest of lead, pending the acquisition of sufficient gold to replace the lead. Thus construed, Medicine seems to us to acquire its proper position among allied sciences, while the many investigators who have devoted their life to its welfare and progress also find their labors fitly represented in its annals. Indeed, the list of these patient workers should be greatly increased if the views submitted in this volume are sound, for the data contained therein—the very ones that have presented the strongest claims to recognition—were found in literature of the kind that often lies dormant many years before its true worth is brought to light. That thousands of such contributions exist we were able to ascertain: an auspicious feature of our earlier work, which showed that we were not dependent upon the "observations and experiments" the future alone would contribute to begin the elimination of "theoretical systems" and replace them, if possible, with others of a more durable kind.

Our earlier investigations included a careful review of prevailing doctrines concerning the nature of vital processes, particularly in respect to the physiological chemistry of cellular metabolism. Notwithstanding our intense desire to acquire elucidative data from the existing literature of the subject, we found it impossible to advance one step beyond the position taken by Professor Foster in 1895 when he wrote: "We cannot trace the oxygen through its sojourn in the tissues. We only know that sooner or later it comes back combined in carbonic acid (and other matters not now under consideration)." To us, this meant a closed door precisely where we hoped to find the information required to fill numerous gaps in our knowledge of the majority of diseases. Tissue-respiration being obviously the dominant factor of all the problems we hoped to solve, we thought it advisable to leave the beaten paths and seek clues among subjects which had never been associated with this physiological function.

Among the subjects which had received attention during our preliminary inquiry was the physiology of the ductless glands. Although the thyroid body had been studied by a larger number of investigators than the adrenals, the latter seemed to us to present a feature directly connected with the problem: *i.e.*, the marked affinity of adrenal extractives for oxygen. We therefore determined to follow the clue this afforded as far as recorded facts would permit, and to trace its connections beyond the field of physiology if possible.

Still, we had little else at our disposal than experiments performed in animals to elucidate the intrinsic functions of these organs. Could such experiments be considered as safe guides in our inquiry? We deemed it advisable to ascertain, first of all, whether the physiological functions of the adrenals were sufficiently similar in all vertebrates to warrant the use of experimental data obtained with lower animals in the study of these organs in man. Such proved undoubtedly to be the case, and we cannot but feel that the results of our investigations—those we will now submit—are based upon solid premises. Indeed, the importance of this fact asserted itself when we were brought to realize that the adrenals could be considered as the key not only to tissue-respiration, but also to the functions of all other organs now classed as "ductless glands." And even these developments assumed secondary positions when it became evident that the better-known organs, such as the heart, lungs, liver, etc., were, so to say, subsidiary structures, the instruments, in a measure, of the smaller "ductless glands," and destined to fulfill the mandates of the latter.

The secretion of the adrenals was traced as far as the pulmonary alveoli, but not beyond. Here it was found to hold in combination the various constituents of hæmoglobin, and to endow both the latter and the plasma with their affinity for oxygen. Prevailing views as to the chemistry of respiration were thus radically transformed, and our knowledge of the manner in which the blood-pigments were held together, likewise. We likewise ascertained that methæmoglobin (hæmatin) and hæmatoporphyrin (hæmatoïdin) were the component bodies of hæmoglobin thus held in association, and that hæmoglobinuria, methæmoglobinuria, and hæmatoporphyrinuria indicated

successive stages of hæmoglobin dissociation incident upon adrenal insufficiency. Again, this portion of the inquiry revealed that, while hæmoglobin absorbed its share of adrenal secretion and oxygen, the plasma did likewise. It thus became evident that the red corpuscles were not the only carriers of oxygen, and that the blood-plasma played an important part in the distribution of this gas. Indeed, we subsequently ascertained that the red corpuscles were secondary factors in this important function, *i.e.*, mere carriers, pack-mules, as it were, and that it was the oxygen-laden adrenal secretion dissolved in the plasma itself which carried on all the oxidation processes of the organism.

Of course, it became necessary to control this assertion. Physiological chemistry was found to afford ample confirmatory evidence, the investigations of Schmiedeberg, Jaquet, Abelous and Biarnés, Salkowski, and others having shown the presence in the plasma of an "oxidation ferment." Claude Bernard had also, many years before, discovered a "ferment" in the blood: the identical substance which Lépine subsequently termed the "glycolytic ferment." These bodies we also found to correspond with our oxygen-laden adrenal secretion —for which, by the way, we would venture to suggest the name *adrenoxin*, though in the body of the present work it is termed everywhere "oxidizing substance."

The many physiological problems awaiting solution then appeared to us in quite a new light. The ease with which the oxygen carried by the plasma could penetrate the minute vascular net-works of all cellular elements not only furnished a clue to the physiological chemistry of the latter, but it also led to the discovery that various structures the functions of which were unknown were in reality blood-channels, or rather plasma-channels. Thus, the axis-cylinders of all nerves and the dendrites of neurons were found to contain a fluid identical to blood-plasma in its reactions to staining fluids. Even the neuroglia-fibrils asserted their identity as plasma-capillaries, the neuroglia felt-work of the substance of the brain and cord representing the intrinsic circulation of these organs. The muscular contractile structures, the various glandular organs, including the liver, pancreas, and spleen, the gastric and in-

testinal glandular elements, etc., were all found to be so disposed as to allow the free circulation of this oxidizing plasma, the red corpuscles passing on in the larger channels. An exception to this rule was found, however, in the heart-muscle: Oliver and Schäfer, as is well known, ascribed to the adrenal secretion the power to contract muscular tissue, and particularly cardiac muscle. We found that contraction of the heart-walls was, in great part, due to this secretion, and that the latter penetrated the heart-substance by way of the Thebesian foramina. The coronary arteries did not lose their functional importance, however; they also were found to supply the cardiac muscle-fibers with oxidizing substance.

Still, the mere presence of oxygen in organic combination in cellular elements did not account, of course, for the physical phenomena witnessed, and it became necessary to ascertain the identity of the agencies with which the oxygen of the plasma combined. In the muscular elements myosinogen proved to be the primary source of residual energy. When combined with the oxidizing substance of the plasma, this organic body liberated, we ascertained, the mechanical energy required for a given contraction, the nerves serving only to incite and govern muscular function. The blood was also found to be supplied with a body similar to myosinogen, *i.e.*, fibrinogen, which likewise combined, but in fixed quantities, with a corresponding proportion of the plasma's oxygen. The fluctuations of the blood's temperature were traced to corresponding variations in the quantities of fibrinogen supplied to the plasma. In the nervous system the immanent source of functional energy was found to be the myelin, or white substance of Schwann, its active constituent being lecithin, composed mainly of hydrocarbons and containing considerable phosphorus. This myelin was not only found to surround the axis-cylinders of all nerves, but also to line the inner surface of the dendrites of neurons and to form the ground-substance of their cell-body. It thus became apparent that the entire nervous system was built upon the same plan: *i.e.*, cylinders containing oxygen-laden plasma surrounded by a layer of myelin, and that the reaction between these two bodies served to form and liberate nervous energy.

The overwhelming importance of the internal secretion

of the adrenals having been determined, the functions of the other ductless glands were studied. Our investigation then showed that the adrenals were directly connected with the *anterior pituitary body* through the solar plexus, the splanchnic nerves, and the cervico-thoracic ganglia of the sympathetic. Indeed, this diminutive organ, hardly as large as a pea, and now thought to be practically functionless, proved to be the most important organ of the body, as governing center of the adrenals, and, therefore, of all oxidation processes.

In general diseases what has been termed the patient's "vitality," or "vital resistance," thus became ascribable to fluctuations in the anterior pituitary body's functional efficiency. In other words, overactivity of this organ, by correspondingly enhancing the production of adrenal secretion, was found to increase metabolism and the activity of all functions in proportion; while depression of its normal activity, by inhibiting the production of adrenal secretion and thus reducing the quantity of oxygen distributed throughout the entire organism, proportionally lowered the activity of all vital processes. But the manner in which the functional efficiency of this organ was maintained had also to be elucidated. This led us to the *thyroid gland*, whose physiological purpose, we found, was to sustain the functional efficiency of the anterior pituitary body up to a certain standard by means of its secretion: iodine in organic combination. Excessive production of this secretion, by causing overstimulation of the anterior pituitary body, gave rise, when prolonged, to "exophthalmic goiter"; while reduced production of thyroid secretion, by inhibiting the functions of the anterior pituitary body, caused myxœdema. The thyroid gland, the anterior pituitary, and the adrenals were thus found to be functionally united: *i.e.*, to form an autonomous system, which we termed the "adrenal system."

Further investigation in this direction showed that the action of thyro-iodine upon the anterior pituitary body represented that of *any* poison introduced into the blood-stream. In other words, it became evident that, instead of acting directly upon the blood or cellular elements, poisons either stimulated or depressed the functional activity of the adrenal system, thus increasing or reducing the production of adrenal

secretion, and, therefore, of oxidizing substance in the plasma. Radical changes in prevailing doctrines as to the manner in which general infections, or other forms of poisoning, produced their effects on the organism thus seemed to impose themselves. In fact, the mass of confirmatory evidence found on all sides (including the effects of removal of the adrenals, the thyroid, or the anterior pituitary body, and of the use of adrenal and thyroid extracts) proved to be incontrovertible. We were thus led to conclude that what are now considered as symptoms of infection or poisoning are all manifestations, more or less severe, of *overactivity or insufficiency of the adrenal system.* Indeed, *the physiological action of remedies was also traced to the anterior pituitary body,* the governing center of this system.

The bearing of this discovery upon the prevailing interpretation of the pathogenesis and treatment of disease is well shown by the manner in which it at once elucidated our knowledge of even the greater scourges of humanity. The symptomatology of Asiatic cholera, for example, was found to be a counterpart of the symptom-complex of advanced adrenal insufficiency, and due to the effects of cholera-toxins upon the anterior pituitary body. The only treatment of any value whatever, as is well known, is early and active stimulation: *i.e.,* the use of agents which, as does the thyroid's active principle, reawaken the functional activity of this organ. Cholera infantum, arsenic poisoning, various toxalbumins, and other intoxications produce identical symptoms; all these proved likewise to be syndromes due primarily to adrenal insufficiency. Pulmonary tuberculosis also asserted its identity as a disease due to lowered functional activity of the adrenal system: either inherited or acquired. While "lowered vitality" had become the result of such a state; here it meant, besides, impaired *cardiac* activity and a corresponding malnutrition of the pulmonary tissues, the underlying factor of vulnerability to the effects of the tubercle bacillus. Our main resource, a high altitude, enhances, we well know, the heart's activity and simultaneously the nutrition of the lungs themselves, as well as that of all other organs, including those of the adrenal system. A multitude of agents have been found helpful in this dread disease, including Koch's tuberculin. All proved to be

adrenal stimulants. Syphilis likewise revealed itself as due to adrenal insufficiency. Here, however, it was of gradual development, the terminal stages being attended with actual death of circumscribed areas of the peripheral tissues: those, indeed, most liable to succumb to denutrition. In "secondary" syphilis a powerful stimulant of the adrenal system, mercury, is efficacious; later on, in the "tertiary" form, a still more powerful agent is required, *i.e.*, Nature's own stimulant: iodine.

We were also led to conclude, in this connection, that the majority of drugs, toxins, physiological toxalbumins, etc., *stimulated* the adrenal system, when the proportion of these agents in the blood did not exceed a certain limit, and that when this limit was exceeded, *i.e.*, when the dose administered, or the amount of toxins secreted by bacteria, etc., was excessive, it either *inhibited* or *arrested* the functions of this system. A large dose of quinine may, for instance, cause adrenal overactivity, a flushed face, a bounding pulse, etc.; but, if the dose is excessive, it will overwhelm the adrenal system, the signs of which are always similar, *i.e.*, pallor, a weak and rapid pulse, etc. Pneumonia illustrates a similar course of events, but due to toxins; the erethic stage exemplifies excessive functional activity of the adrenal system: a protective process, "fever," having for its purpose the conversion of pathogenic elements into benign waste-products by cleavage and oxidation. When the proportion of toxins increases notwithstanding this protective function, the adrenal system lapses into insufficiency, that stage during which active stimulation—of the adrenal center, the anterior pituitary body—is our sheet-anchor.

This brought to light a number of diseases: tetanus, epilepsy, hydrophobia, septicæmia, eclampsia, and kindred disorders, in which symptomatic treatment could prove harmful. In tetanus, for example, the convulsions normally suggest the use of cannabis Indica, the bromides, etc., as sedatives or depressomotors. In the light of our views, precisely the opposite course is indicated, *i.e.*, active stimulation of the adrenal system, because the convulsions are not due to the tetanus toxins, but to accumulated waste-products. Indeed, the effect of this toxin is to gradually reduce the efficiency of the adrenal system and of all oxidation processes accordingly. The present mortality

of tetanus sustains us, especially when compared with the results of Baccelli's carbolic-acid treatment. As interpreted from our standpoint, this agent powerfully stimulates the adrenal system, and simultaneously causes prompt oxidation of the waste-products. Baccelli, we know, saves almost all of his cases. The same may be said of hydrophobia; here again the method of treatment employed in the various Pasteur Institutes insures precisely what Baccelli does with the aid of carbolic acid: in suitable doses, the extract of desiccated cord injected raises the anterior pituitary body's functions to their normal standard and sustains them until all danger is past.

The element of specificity would seem to be lost with the anterior pituitary body as the source of all symptomatic phenomena. But such was not found to be the case by any means. The adrenal system showed itself as the source of a large number of symptoms, but not of all. Each pathogenic agent, a toxin, a vegetable poison, a venom, for example, influences the adrenal center in its own way. Some drugs—quinine, for instance—are able to raise the adrenal system's functional activity to a very high state before they cause it to lapse into insufficiency; others, such as hydrocyanic acid, almost at once overwhelm it. Between these two extremes are many degrees of functional activity, each of which gives rise to symptoms essentially ascribable not only to the adrenal system itself, but also to other organs which are gradually awakened to inordinate activity as the oxidation processes become more active. Among these other organs, the *posterior* pituitary body (or infundibular lobe of the hypophysis), the spleen, and the pancreas, require special mention in this connection, since we found them to be endowed with functions which had not so far been discerned.

The *posterior pituitary body*, far from being the insignificant vestigial organ it is generally thought to be, was found by us, thanks mainly to the investigations of Berkley, Andriezen, Howell, and de Cyon, to stand second in importance only to its mate, the anterior pituitary body. Indeed, it proved to be the *chief functional center of the nervous system*, its numerous groups of neurons forming the starting-point, or highly specialized center, of a single class of nerves. The various

medullary centers thus became mere connecting nuclei, which, stimulated or injured, however, could become the source of all the morbid phenomena recorded by physiologists. The posterior pituitary body also proved to be the center upon which all emotions, shock,—psychical or traumatic,—and kindred sources of excitement or depression react, impairment of its functions accounting for the pathological phenomena now ascribed to such causes. Again, as the general center of the nervous system, it was found to be the anterior pituitary body's co-center in sustaining the cellular metabolism of all organs. While the anterior pituitary body insured oxygenation of the blood through the adrenal secretion, the posterior pituitary body adjusted and governed the functional activity of all organs through the nervous system. This accounts for the fact that both cerebral hemispheres can be removed from various animals without materially impairing the functions of their motor, vascular, respiratory, and nutritive systems. But it also suggests that an organ so sensitive to external impressions should likewise be easily influenced, directly or indirectly, whenever pathogenic agencies, poisons, drugs, etc., are present in the blood. Indeed, we ascertained that the posterior pituitary was an important feature of the morbid process in influenza, hay fever, hysteria, catalepsy, and other obscure affections.

The *pancreas and spleen* may be considered jointly, since, as long ago asserted by Schiff, the secretions of these two organs unite in the formation of a powerful proteolytic ferment, a process subsequently defined by Herzen as the one leading to the conversion of trypsinogen into trypsin: the albumin-solving constituent of the pancreatic juice. While confirming this view, our own analysis led to the conclusion that, in addition to the trypsin supplied to the intestinal canal, a portion of this ferment passed into the splenic vein as an *internal secretion* and thence into the portal vein. We also ascertained that this ferment played a leading part in all immunizing processes, its main function in the blood-stream being to destroy toxic albuminoids. These, as is well known, include all toxins and diastases secreted by bacteria, proteids, toxalbumins, vegetable poisons, and venoms.

Immunity, or rather the various subjects usually grouped

under this heading, seems to us to have also acquired a number of elucidative factors. The investigations of Metchnikoff, Ehrlich, Bordet, Pfeiffer, and others were not only sustained in many particulars, but the solidity of many of their deductions was shown by the fact that the addition of considerable new evidence only served to harmonize their views. Phagocytosis proved to be the preponderating factor of immunizing processes; but the spleno-pancreatic internal secretion, trypsin, to which we have just referred as the organic body which reduced toxic albuminoids to inert cleavage products, was found to be the agency which digested bacteria in the digestive vacuoles of phagocytic leucocytes. Indeed, Metchnikoff had found this body to be a trypsin.

The multiplicity of antitoxins, cytolysins, and haptophore groups which Ehrlich connected with his side-chain theory no longer seemed necessary in the light of our views, the diversity of effects due to toxins, as in the case of poisons, drugs, etc., being ascribable to sundry factors, and especially to variations in their toxicity. Rid of these confusing elements, Ehrlich's labors appeared to us in a new light. His amboceptor (Bordet's sensitizing substance) proved to be our oxidizing substance, and his complement (Buchner's alexins, Metchnikoff's cytases) became our spleno-pancreatic internal secretion: trypsin. But we were led, in addition, to ascribe to an organic body which we have already mentioned, fibrinogen, a preponderating part in the process through which all albuminoid poisons (including toxins) and bacteria are converted into benign products in the blood. Indeed, we found that this process required the simultaneous co-operation of the *three* agencies named, trypsin only becoming sufficiently active as a proteolytic agent in the presence of given proportions of oxidizing substance and fibrinogen. Insufficiency of either of these three bodies was found to compromise the issue of the disease in which it occurred. In typhoid fever, for instance, fibrinogen was shown by our investigation to be the missing agency; in diphtheria it was trypsin which was found absent from the blood-stream. Indeed, the dominant active principle of antitoxin proved to be trypsin.

The white corpuscles of the blood were found to be en-

dowed with functions greatly exceeding in importance any as yet ascribed to them even hypothetically. Our researches showed that these cells supplied the organism with the agencies that combine with the oxidizing substance to insure the continuation of life and the efficiency of all organic functions. The neutrophiles, Metchnikoff's wandering phagocytes, were traced from the solitary and agminated follicles to the cavity of the intestine, where they ingested proteids; then through the villi, mesenteric veins, and portal veins, where they absorbed the spleno-pancreatic secretion, *i.e.*, the trypsin which Metchnikoff found them to contain. These cells formed, we ascertained, *peptones, myosinogen,* and *fibrinogen*—all globulins—from the proteids ingested by them and distributed these products to all tissues, the muscles, and the blood itself. Ehrlich's eosinophiles, non-phagocytic leucocytes, asserted their identity as daughter-cells, the separation from their parent-cells, the neutrophiles, occurring in the liver by mitosis. They were traced to the pulmonary alveoli, where they participated in the formation of the nucleated epithelium. Their product proved to be *hæmoglobin.* The basophiles were found to take up fats derived from foodstuffs which penetrated the lacteals and lymphatic ducts, to convert them into *myelin* granules, and to distribute them throughout the entire nervous system.

As these three varieties of leucocytes (all other varieties being probably immature cells) were traced to the right auricle, either through the inferior or superior vena cava, the presence of all three in the lungs appeared necessary as controlling evidence. Indeed, Virchow, Wagner, Cohnheim, Lenhartz, and others had referred to their presence in sputum without knowing their original source. The "myelin droplets" of Virchow, or "crushed nerve-substance" of Lenhartz, are familiar features of this subdivision of pathology.

Briefly, our inquiry seems to us to have shown that the adrenal system is the source of the secretion which, with the oxygen of the air, forms the oxidizing substance of the blood-plasma. It has also revealed, we believe, the origin and mode of distribution of the bodies with which this oxygen directly or indirectly combines: *i.e.*, peptones, myosinogen, fibrinogen, hæmoglobin, and myelin, to insure the continuation of life and

the efficiency of all organic functions. Finally, it has suggested that in addition to these agencies, all leucocytes and, under certain circumstances, the plasma, contain a protective agency, trypsin, which, with Metchnikoff's phagocytic cells, serves to destroy micro-organisms and convert their toxins and other albuminoid poisons into harmless products. Considered jointly, these various factors seem to us to represent the aggregate of vital phenomena.

We have termed "Immunizing Medication" the use of remedies to arrest diseases during their incipiency by stimulating the functional activity of the adrenal system. Indeed, in the light of our views, it becomes evident that during epidemics, after injuries received in places thought to contain tetanus saprophytes, after bites of presumably rabid animals or venomous animals, or after infections of any sort, we can cause in our blood-stream a sufficient accumulation of phagocytes, trypsin, fibrinogen, and oxidizing substance to offset the lethal tendency of these pathogenic elements. But it is not only in acute affections that protection can thus be acquired. Inherited vulnerability to tuberculosis, for example, is, in truth, nothing but congenital adrenal insufficiency, a low grade of general nutrition, which it is within our power to correct by the appropriate use of the many remedial agents which science has placed in our hands.

The main cause of death during acute diseases was also studied. Not only were the classical teachings regarding the importance of the blood's alkaline reaction emphasized; but the very fact that the various leucocytes were found to distribute their peptones, myosinogen, fibrinogen, etc., by migrating in every direction, raised the need of an adequate proportion of alkaline salts in the blood-stream to the position of a *sine qua non* as regards the continuation of life, especially in febrile disorders. Indeed, the rapid utilization of alkaline salts, especially sodium chloride, in the organism, and the fact that they are inadequately, if at all, replaced through their normal channel, the digestive tract, during disease, proved to be the predominating cause of death.

The foregoing summary can only be said to include some of the more important processes, physiological and pathological,

studied in this volume. A comprehensive study of the nervous system and of the functional processes in the various organs, as modified by the presence of previously unrecognized structures, the formation of glycogen, urea, etc., the protective processes in the intestinal canal and respiratory surfaces, could not be satisfactorily summarized. The same may be said of Addison's disease, acromegalia and chlorosis, the pathogenesis of fever, the identity of the Widal reaction, the so-called gouty diathesis, glycosuria, cancer, the causes of the predilection of children to certain infectious diseases, the action of a large number of remedies upon the adrenal system, etc.

Can we pretend that, owing to the care with which our investigations have been conducted, our deductions are invulnerable? We only formulate this question to answer it negatively. The working methods adopted, however, do not seem to us to have rendered any serious deviation from the straight path possible. All theories, even those advanced by all the greatest authorities of the nineteenth century, were totally ignored. Our purpose being to treat each question as if it had been a mathematical problem, positive data were alone used as factors. Preconceived conclusions were under no circumstance allowed to prevail, and the solutions were only formulated after each question had first been submitted to analysis, then to a reconstructive, or synthetic, process.

We fully realize, however, that our factors were necessarily drawn from a mere fraction of existing literature,—though a vast amount of the latter had to be scrutinized,—and that the balance of recorded data and future work of the galaxy of brilliant workers which our profession contains in all lands may eventually completely transform our views. Again, we do not lose sight of the fact that our short-comings may have caused us to present distorted images simply through our limited knowledge of several of the branches of science—physiological chemistry, for instance—to which we have had recourse for light. Yet, if our aim is properly interpreted, it will become apparent that we have encompassed the whole field of medical science in our labors, in the hope that a broad horizon would enable us to discover its weaker parts.

We found, we may say, that the back-bone of Medicine was

the absent factor, and that if the patient labors of so many great minds had not proven as useful in the development of practical medicine as they should, it was because they lacked such a fundamental frame-work to afford a fixed *nidus* for each discovery, wherein its true relation to other discoveries would at once become evident. What details we have introduced, therefore, only had for their purpose to show that the newer organic substances described—the oxygen-laden adrenal secretion of the plasma, for example—were inherent parts of the organism as a whole. What we have said of the physiological chemistry of glycogen, myosinogen, urea, and many other bodies, may not stand the scrutiny of an Ehrlich, a Gautier, an Abel, a Chittenden, a Vaughan; but the fact that such men are available to promptly correct what errors we might have made gave us the confidence to proceed with our work without undue anxiety. We did our utmost, with what limited knowledge we possessed of these various auxiliary branches of medicine, to clearly set forth our views, and will accept with gratitude any warranted correction which our fellow-workers may deem necessary.

That our conception of the functions of the ductless glands is well grounded seems probable. Had it been otherwise, the existing concordance between the various parts of the work could not have been obtained; nor would solidly established data have fallen normally into line without requiring hypothetical functions to establish their usefulness in the elucidation of the many questions which our investigation awakened. If we are not mistaken, this affords in itself the kind of evidence which betokens sound premises.

We may also venture the opinion that, if our views are based on a firm foundation, our labors have served to illustrate the dangers of promiscuous self-medication indulged in by the general public. Indeed, we will have occasion to show, in the second volume, that vulnerability to disease may not only be thus acquired, but that the adrenal system, when debilitated through injudicious stimulation, is unable to protect the organism when disease is initiated.

In addition to periodical literature, a large number of books were consulted. Among these, however, two have been

quoted very frequently in this volume, namely: Prof. Michael Foster's "Physiology" and Prof. Horatio C. Wood's "Therapeutics," two masterpieces of their kind. Experimental therapeutics, with which Professor Wood's name is so intimately associated, afforded information which not only proved invaluable in the course of our inquiries, but without which several of the more important conclusions submitted could hardly have been reached. Indeed, while foreign countries, especially France, Germany, Great Britain, Italy, and Russia, have contributed the greater part of the evidence which has formed the groundwork of our deductions, much of the best and soundest work quoted, we are pleased to state, originated in our own country.

The subjects treated in this volume appear in the order in which they were studied. The many new lines of thought discussed could thus be made to start with familiar facts and be gradually developed. The earlier data and deductions submitted, therefore, should only be considered by the reader as inherent factors of conclusions to be reached later on.

Brown-Séquard's labors may be said to have laid the foundation of this work. We little thought, when we met him last, at the Institute of France, that the only expression of gratitude available to us when this volume would be finished, would be a dedication to his memory!

Special pharmacodynamics and physiological pathology, both subdivisions of Applied Therapeutics (a department of Medicine to which we expect to devote our special attention, henceforth, both in our practice and in research work), will be considered in the second volume, which will appear a few months after the present one. The latter will also contain an Analytical Index, in which the modifications in prevailing doctrines that our labors may have suggested will be systematically arranged.

Our thanks are due to our publishers, the F. A. Davis Company, and to the manager of their printing department, Mr. Van Horn, for the care given to the mechanical preparation of this work.

C. E. de M. Sajous.

Philadelphia,
January 1, 1903.

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CHAPTER I.

THE PHYSIOLOGY OF THE ADRENALS AS VIEWED FROM THE STANDPOINT OF CLINICAL PATHOLOGY.

SIMILARITY OF THE EFFECTS OF REMOVAL OF THE ADRENALS IN ALL VERTEBRATES, INCLUDING MAN.

Brown-Séquard,[1] in 1856, demonstrated the physiological importance of the suprarenal capsules by showing that removal of these organs from animals was soon followed by death. To offset the conclusions of Phillipeaux and Gratiolet, who ascribed death to secondary involvement of the central nervous system, he extended his researches,[2] and showed, first, that transfusion of blood taken from a normal animal into a dying, decapsulated animal brought the latter to life, and, second, that the blood of a dying, decapsulated animal was poisonous to another decapsulated animal, the life of the latter being shortened by eight hours as compared to the average longevity of other animals similarly mutilated.

A certain degree of antagonism to Brown-Séquard's conclusions still prevails among a limited number of investigators, who ascribe death in animals from which both adrenals have been extirpated to surgical shock: a view apparently sustained by the close relationship that exists between these organs and the sympathetic system. That such may be the case under some circumstances: *i.e.*, the use of an animal debilitated by starvation or rough handling, lack of dexterity in the extirpation of the organs, is to be surmised; but when all features that tend to compromise the issue are absent, there appears to be no ground for the view that shock is the cause of death in decapsulated animals. As shown by Langlois,[3] no marked symptoms usually occur during the first twenty-four hours. The fatal

[1] Brown-Séquard: Comptes-Rendus de l'Académie des Sciences, vol. xviii, 1856.

[2] Brown-Séquard: Journal de Physiologie, vol. i, 1858.

[3] Langlois: Archives de Physiologie norm. et path., vol., 1897.

issue is not immediate; and in frogs, rabbits, guinea-pigs, and dogs the post-operative life varies from an average of forty hours in mild weather to twelve or thirteen days in the hibernating frog in winter. In a series of fifty-nine rats from which Boinet[4] removed both adrenals, four lived several months. Some evidence of shock should have appeared in at least a small proportion of the operated animals. Not only was this not the case, but the fact that in four of them the prolongation of life was found to have been due to accessory or compensatory organs demonstrates the weakness of the shock hypothesis as the main cause of death in decapsulated animals. Furthermore, the average symptomatology of post-operative life in various species—inco-ordination, muscular weakness or excitement, and tremors; then paralysis of the hind-quarters, with gradual involvement of the trunk and upper extremities, contraction of the pupil, gradual and steady slowing of the cardio-vascular rhythm, convulsions, hæmaturia, epistaxis, etc.—in no way resembles that of shock.

Finally, complete removal of but one organ seems to affect animals so slightly that they appear to suffer no inconvenience; they continue to live month after month, "quite well and active"; *i.e.*, until the experimenter removes the second adrenal, when death occurs within thirty-six hours. This fact, added to many others elucidated by the labors of Abelous and Langlois,[5] Oliver and Schäfer,[6] Cybulski,[7] Szymonowicz,[8] Gourfein,[9] Langlois,[10] Swale Vincent,[11] Boinet,[12] A. G. Auld,[13] among others, suggests that there is no legitimate ground—after eliminating all factors that obviously tend to disguise the source of physiological phenomena and pervert their meaning—to doubt that, as Brown-Séquard was first to show, extirpation of both

[4] Boinet: Marseille Médical, Sept. 1, 1899.

[5] Abelous and Langlois: Archives de Physiologie norm. et path., vol. xiii, p. 267.

[6] Oliver and Schäfer: Journal of Physiology, vol. xviii, 1895

[7] Cybulski: Gazeta Lekarska, March 23, 1895.

[8] Szymonowicz: Archiv f. d. Gesam. Phys., vol. lxiv, 1896.

[9] Gourfein: Revue Médicale de la Suisse Romande, March, 1896.

[10] Langlois: *Loc. cit.*, 1898.

[11] Swale Vincent: Journal of Physiology, Sept. 11, 1897; Feb. 17, 1898; Apr. 25, 1898.

[12] Boinet: *Loc. cit.*

[13] A. G. Auld: British Medical Journal, June 3, 1899.

suprarenals is followed by death, and that these organs fulfill in the organism a rôle of great physiological importance.

Are the suprarenal glands functionally as important in man as they are in the lower vertebrates? The clinical field alone offers the necessary elements for the study of this question; but it is strewn with obstacles. The various kinds of neoplasms which develop in these organs, with the possible exception of sarcoma, are of slow growth; the sufferer passes through various phases that are more or less influenced by concomitant conditions and by the pressure which the tumor exerts upon important neighboring structures. In carcinoma there may also be involvement of other viscera by continuity of tissue or metastasis. We therefore obtain, in relation to the symptom-complex of pure suprarenal origin, a transformed picture, one that precludes all certainty as to the relations between cause and effect. Addison's disease affords, if anything, less opportunity for solid analysis; it may be associated with suprarenal lesions and it may not; in some cases but one organ is involved; in others, both; if it is due to suprarenal tuberculosis, this process may be secondary or primary, thus furnishing a series of misleading symptoms due to the extrinsic lesions; finally, we may at a *post-mortem* find the organs completely destroyed and obtain an *ante-mortem* history in which the Addisonian syndrome is conspicuously absent.

What is required for a fruitful analysis of this question is a condition in which the adrenals are alone the seat of a mortal lesion: a lesion capable of suddenly annihilating the functions of both organs precisely as does their experimental removal in animals. A single disorder of the adrenals, among the few that have been so far described, fulfills these requirements in some of its manifestations, namely: hæmorrhage. The literature of this subject is, however, exceedingly meager: hardly one hundred cases having been reported. We are therefore fortunate in having at our disposal an able and exhaustive review of eighty of these cases, including several of his own, by François Arnaud,[14] of Marseilles, which afford the necessary data. While some of the cases are very briefly reviewed, the

[14] François Arnaud: Archives Générales de Médecine, p. 64, July, 1900.

details furnished are at least sufficient to enable us to obtain what appears to be strong evidence to the effect that, precisely as it does in the lower animals, destruction of the adrenals in man causes death within a very brief period.

Indeed, out of the eighty cases collected by this investigator, death occurred within a period ranging from a few hours to three days in fifteen. In all of these the pathological data given show that both glands had been the seat of the hæmorrhagic process: of "suprarenal apoplexy," as he terms it. Ten of these cases, however, lose some of their value as testimony because no allusion is made to the condition of the other organs. In the other five, including details that we have obtained from the original reports, it is specifically stated that *lesions were found nowhere else in the organism.* To the following tabulated list of these cases we have added two recently reported (Andrewes and Colman):—

Case 1 (Arnaud[15]).—Male, 36 years. Death occurred 48 hours after entrance. Both glands were apoplectic and greatly enlarged. One weighed 28 $^1/_2$ grammes; the other 48 grammes. Both when cut resembled flesh, and were studded with hæmorrhagic foci and spots of hæmatomatous organization indicating a progressive lesion of long standing. A small amount of medullary substance was still present in the right capsule, but otherwise the organs were structurally destroyed.

Case 2 (Arnaud[16]).—Female, 17 years. Death occurred suddenly on the eleventh day after the receipt of a burn on the arm; the symptoms suggested acute poisoning, but the autopsy revealed hæmorrhage into the right capsule and congestion of the left.

Case 3 (Andrewes[17]).—Female, 15 months. Death 36 hours after onset of symptoms. Both capsules showed interstitial hæmorrhage. All cultures were sterile, or, if any organisms were present, not one grew on ordinary media or stained with ordinary reagents.

Case 4 (Mattei[18]).—Male, aged 60 years. Death in 24

[15] Arnaud: Archives Générales de Médecine, pp. 16 and 53, July, 1900.

[16] Arnaud: Archives Générales de Médecine, p. 50, July, 1900.

[17] Andrewes: Lancet, May 7, 1898.

[18] Mattei: Lo Sperimentale, 1863. Case I in Trans. Gaz. hebdom., Paris, No. 35, p. 380.

hours after onset of acute symptoms. Both capsules were enlarged, and transformed into bags containing clots surrounded by the cortex, which had thus been forcibly detached from the medullary substance.

Case 5 (Garrod and Drysdale[19]).—Case, aged 4 months. Brought into hospital dead. Both glands dark-purplish red, though not enlarged; meshes of stroma filled with red corpuscles.

Case 6 (Droubaix[20]).—Case, 11 hours old at onset of symptoms. Death in 3 days. Hæmorrhage into both organs, with infiltration into the pericapsular cellular tissue.

Case 7 (Colman[21]).—Case, 11 months. Death in about 25 hours. Both capsules showed diffuse interstitial hæmorrhage, and cultures proved sterile.

Strongly suggestive, also, is the fact that, of the seventeen cases of comparatively sudden death, fifteen showed suprarenal apoplexy in both organs, while two only showed involvement of but one organ. These two instances might invalidate the evidence adduced, could the sudden death in them not be shown to have been due to other causes. But such is the case: In the one (Parrot's[22] case No. 11) the hæmorrhagic adrenal had ruptured, and the patient died of hæmorrhage into the peritoneal cavity; in the other (Droubaix's[23] case No. 9) death had resulted from uræmia, due mainly to granular and cystic kidneys.

Additional evidence is afforded by the fact that complete destruction of but one adrenal proves harmless to man, as it does in animals. The results of operative procedures instituted for the removal of suprarenal neoplasms prove this to be the case. A lipomatous capsule, for instance, was removed, along with a wedge-shaped piece of underlying kidney, by Mayo Robson[24] in 1897. "The wound healed by first intention and the patient rapidly regained her lost flesh and strength. She remains well, and had had no return of the trouble." This

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[19] Garrod and Drysdale: Lancet, May 7, 1898.
[20] Droubaix: Thèse de Paris, Case I, p. 26.
[21] Colman: Lancet, May 7, 1898.
[22] Parrot: Archives Générales de Médecine, vol. xcix, 1872.
[23] Droubaix: Thèse de Paris, 1887
[24] Mayo Robson: British Medical Journal, Oct. 21, 1899.

report was published almost two years after the operation. A fibromyxosarcomatous adrenal was removed, along with the entire right kidney, by Howard A. Kelly.[25] The case proceeded to full recovery notwithstanding the malignant nature of the growth. A tuberculous adrenal and the right kidney were also removed by A. F. Jonas.[26] The patient was discharged six weeks later in full convalescence. Finally, Knowsley Thornton[27] removed a sarcomatous gland from a woman aged 56 years. The patient was seen six years later and found in good health.

This does not mean, however, that a diseased gland may not cause death. In this particular the adrenals are similar to any other organ. A rapidly growing sarcoma or a carcinoma may start in one of the organs, develop by metastasis elsewhere, and cause death. Tuberculosis frequently finds a *nidus* in either adrenal or both simultaneously; this process, along with the asthenia engendered by the suprarenal disease, may rapidly end in death. Again, when we consider the frequency with which fatty degeneration is found in these organs when microscopically examined,—thirty-six times out of one hundred autopsies taken *at random,* according to Arnaud,[28]—it would certainly be unwise to establish such limits.

But this also suggests that death may thus follow any destructive process (hæmorrhage included) of a single adrenal, if the functions of its mate are sufficiently inhibited through a local lesion or by a morbid condition involving its peripheral vascular or nervous supply. Indeed, the anatomical relations of these glands indicate that their functions are primarily dependent upon the integrity of these trophic structures. The multitude of nerves distributed to them include medullated fibers from the solar plexus, the sympathetic's densest network. Dogiel[29] states that the internal zone of the cortex is surrounded by a more or less dense fibrillary plexus, and that the medullary substance is supplied with an extraordinary sup-

[25] Howard A. Kelly: Quoted by Ramsay, Johns Hopkins Hosp. Bull., Jan., Feb., Mar., 1899.

[26] A. F. Jonas: Annals of Surgery, April, 1898.

[27] Knowsley Thornton: Harveian Lectures.

[28] Arnaud: *Loc. cit.*, p. 6.

[29] Dogiel: Archiv f. Anatomie u. Physiologie, p. 90, 1894.

ply of nerves. He likewise found the aggregate of these nerve-fibrils to be greater than that of the glandular elements proper. It seems evident, therefore, that any organic lesion affecting or involving the peripheral nerve-structures of one organ—tuberculosis, cancer, etc.—can so compromise its functions as to make it practically useless if suddenly called upon by hæmorrhage into its mate to assume the physiological rôle of both.

All these facts appear to demonstrate that in man, as well as in the lower vertebrates, life continues as long as one of the adrenals is normal, or, at least, as long as any morbid condition affecting this organ intrinsically or extrinsically is not sufficiently advanced to materially compromise its physiological functions. But, as is also the case in lower vertebrates, man soon dies if the physiological functions of both organs are arrested through any intrinsic or extrinsic disorder, unless some compensating organ or condition be vicariously active. It seems evident, therefore, that *the physiological functions of the adrenals are sufficiently similar in all vertebrates to warrant the use of experimental data obtained with lower animals in the study of these organs in man.*

FUNCTIONS OF THE ADRENALS THAT ARE SUPPRESSED WHEN THESE ORGANS ARE REMOVED.

Cybulski and Szymonowicz[30] found that blood drawn from the suprarenal vein gave rise, when injected into the blood-stream of normal animals, to manifestations similar to those observed after the injection of suprarenal extract. As a controlling experiment, these observers also injected blood taken from veins other than the suprarenal, but with negative results. Langlois[31] corroborated these observations as regards the effects of blood obtained from the suprarenal vein. Dreyer[32] reached the same results, though not in all animals: a feature of his experiments easily accounted for by the known fact, referred to by Howell, that the amount of substance produced by the organs may vary at different times and under different

[30] Cybulski and Szymonowicz: *Loc. cit.*
[31] Langlois: Archives de Phys. norm. et path., p. 152, 1897.
[32] Dreyer: Cited by Howell, *loc. cit.*

circumstances. This obviously suggests that the morbid phenomena witnessed after extirpation of the adrenals are due to the absence of a substance produced by these organs and secreted into the suprarenal veins.

Not only do the adrenals produce the blood-pressure-raising substance the lack of which accounts for the symptoms that follow bilateral removal, but the secretion of these organs alone possesses the property of arresting these symptoms. Cybulski[33] experimentally found that the increase of blood-pressure and other cardio-vascular manifestations, etc., could not be obtained from similar preparations from the brain, spinal ganglia, lymph-glands, liver, spleen, kidney, testicle, or thyroid. Mankowsky[34] corroborated these observations and noted that the blood-pressure-raising power was peculiar to the suprarenal extract, his experiments having also shown that this action could not be obtained from the fresh thyroid gland, pancreas, lymphatic glands, parotid, kidneys, liver, spleen, cerebrum, heart, or skeletal muscles.

An extract obtained from human adrenals possesses similar properties to the preparations in general use. This important fact was ascertained by Guinard and Martin, of Lyons,[35] who conducted a series of experiments with the adrenals of a healthy executed criminal. Expressed juice of these glands "produced physiological phenomena similar to those noted with the extracts from organs obtained from other animals. The nature of the poisons contained in them did not appear to differ."

The following conclusions therefore appear to be warranted:—

1. Removal of both adrenals arrests the supply of a secretion which these organs pour into the suprarenal veins.

2. The secretion of the adrenals gives rise to physiological phenomena which are not awakened by the active principles of other organs.

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[33] Cybulski: *Loc. cit.*

[34] Mankowsky: Russian Archives of Physiology and Bact., March, 1898.

[35] Guinard and Martin: Journal de Physiologie et de path. génér., 1899; Archives Générales de Médecine, Oct., 1899.

EFFECTS OF THE ADRENAL SECRETION ON THE CARDIO-VASCULAR SYSTEM.

THE ADRENAL SECRETION AND THE INHIBITORY CENTERS.—While removal of both adrenals is followed by a great fall of blood-pressure and very feeble and rapid cardiac action, intravenous injections of suprarenal extract invariably cause marked increase of the blood-pressure and equally marked slowing of the heart-beat. The blood-pressure increase thus appears to be due to the direct effect of the specific suprarenal principle; but to account for the slowing of cardiac action we are led to implicate the inhibitory action of the vagus. If the bulbar center of this nerve be paralyzed by atropine, however, or the vagus itself be cut, this inhibition ceases and quickening of the heart-beat follows, accompanied by a still greater increase of blood-pressure. Oliver and Schäfer found[36] that the inhibitory action was exerted mainly upon the auricles, their beats becoming gradually weaker; while the ventricular contractions, though slower, were, in reality, stronger.

Mooted points have arisen in this connection that have entailed considerable divergence among physiologists; and, curiously enough, when the various views entertained are analyzed, none of them seem to harmonize with available experimental data.

Cybulski,[37] after a series of careful experiments, reached the conclusion that suprarenal extract acted upon the vasomotor centers of the medulla and spinal cord, first stimulating, then paralyzing, them. Oliver and Schäfer,[38] after equally careful experiments, concluded that the extract induced reflex stimulation of the inhibitory center by first causing powerful constriction of the arterioles. This they thought accounted for the slowing of the heart observed before the vagi were cut, and physiologists have generally accepted the conclusion that the inhibitory center is stimulated. Indeed, even the more recent—and carefully conducted—physiological researches have sustained this opinion; Wallace and Mogt,[39] for instance, were

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[36] Oliver and Schäfer: Journal of Physiology, xviii, 1895.
[37] Cybulski: Gazeta Lekarska, March 23, 1895.
[38] Oliver and Schäfer: Journal of Physiology, vol. xviii, p. 230.
[39] Wallace and Mogt: American Physiological Society Proc., Dec. 28, 1898.

led by unquestionable experiments to conclude that the suprarenal extract stimulated the vagus center, thus inhibiting the heart.

A second set of divergent views refers to the nervous structures involved when the heart is separated from its inhibitory center by section of the vagus. The influence of the extract, in this connection, is ascribed by Mankowsky[40] to stimulation of the cardiac and respiratory centers; by Gottlieb,[41] to the direct stimulating effects of the substance upon the intrinsic cardiac ganglia; by de Cyon,[42] to some action upon the vasoconstrictor nerves and simultaneously upon the central and peripheral ends of the cardiac accelerators; by Velich,[43] to stimulation of the vasoconstrictors; and finally by other observers to various more or less complicated combinations which all include some part of the nervous system as the seat of primary effect. By inference, therefore, we are led to look upon this system as the one upon which the specific principle of the adrenals acts physiologically.

The first question, which embodies the divergent views of Cybulski, on the one side, and Oliver and Schäfer, on the other, resolves itself into this: Does the suprarenal active principle act at all upon the inhibitory centers?

It may prove useful in this connection to recall that, according to prevailing doctrines, the functions of the heart are governed by two sets of nerve-fibers. The one set, derived from the splanchnic, increases the vigor of the heart-beat and tends to quicken the number of beats in a given time. The other set, which arises from the vagus, inhibits the vigor of the heart-beats and their rate or rhythm. Both these "augmentor" and "inhibitor" fibers receive their impulses from the medulla oblongata and from a limited area of the upper portion of the cord, and represent the external, or extrinsic, motor-supply of the organ. Again, the medulla and the spinal area referred to receive impulses—including reflex impulses—from all parts of the organism, including the heart proper, and there is thus

[40] Mankowsky: Russian Archives of Pathology, Clinical Med., and Bact., vol. v, No. 3, March, 1898.

[41] Gottlieb: Archiv für exp. Path., Bd. xxxviii, 1896.

[42] De Cyon: Pflüger's Archiv für Physiol., vol. lxii, p. 370, 1898.

[43] Velich: Wiener med. Blatter, Nov. 11, 1897.

established a cycle of afferent and efferent impulses of which the medulla and the portion of the cord immediately below it represent the center. The effects of destruction of these structures can easily be foretold. As shown by Stricker nearly thirty years ago and by other physiologists since, extirpation of the cervical and dorsal portions of the cord causes arrest of the heart's action. When to this is added destruction of the medulla, the certainty of immediate death is but enhanced. Again, certain agents—chloral hydrate, for instance—are known to abolish the functional activity of the cord and to affect the heart as if the vagus had been severed.

Applying these classical data to the question in point, it becomes evident that, if the inhibitor or augmentor centers were directly or reflexly stimulated by suprarenal extract, the effects of extirpation of these centers or of the cord would not be counteracted by its use *since there would be no center to receive and transmit impulses.* The arrest of the heart's action would therefore be permanent.

But experiments have shown that the injection of suprarenal extract at once causes this organ to resume its beats notwithstanding total extirpation of the entire cord. Thus, Biedl[44] cut the medulla oblongata and removed the entire cord of mammals; and, when the blood-pressure had become reduced to 9 millimeters, injected suprarenal extract. This at once brought up the pressure to 160 millimeters. Gottlieb[45] chloralized rabbits until the heart-beats became irregular and excessively slow. An injection of suprarenal extract at once restored the regularity and volume of the pulse. He tried the same experiment when the pulse was no longer registrable by the manometer; a similar result was obtained, and the heart almost immediately resumed its normal action. Isaac Ott[46] etherized a rabbit, cut the cord above the atlas, severed all the cardiac nerves in the neck, and verified the section of the cord *post-mortem.* Injections of suprarenal extract were then used repeatedly as soon as the pressure became greatly lowered. They brought it up from 24 to 144 the first time, from 17 to

[44] Biedl: Wiener klin. Wochenschrift, Bd. ix, 1896.
[45] Gottlieb: Archiv für exp. Path. und Phar., Bd. xxxviii, 1896.
[46] Isaac Ott: Experiment No. 11, Medical Bulletin, Jan., 1898.

134 the second, and from 24 to 124 the third time, the interval between the injections of extract and the highest-pressure marks ranging from fifteen to thirty seconds.

These experiments, to which others of a similar kind could be added, speak for themselves. They distinctly show that *the inhibitory centers are not directly stimulated by the suprarenal extract*, as thought by Cybulski, Wallace and Mogt, Mankowsky, Gottlieb, and other careful observers.

And, indeed, their conclusion is apparently justified, if removal of the medulla and cord is left out of consideration, and with injections of suprarenal extract as an only guide. In other words, to the question—does suprarenal extract directly affect the cardio-inhibitory centers?—an affirmative experimental result on injecting it into mammals—slowing of the heart—would always be obtained, while the crucial test—section of the vagus—would at once confirm the conclusions previously reached by causing great increase in the rapidity of the heart's action. But removal of the vagal centers and the cord in no way preventing the action of the extract, the only logical deduction that imposes itself is that *the suprarenal extract exercises a stimulating action directly upon the cardiac muscle.*

The Adrenal Secretion and the Vasomotor System. —The last deduction submitted necessarily implicates other phases of the question. Prominent among these is the effect ascribed to suprarenal extract upon the vasomotor system by various physiologists and clinicians. Is there any such action? Veins—which are but little, if at all, influenced by the cardiac impulse in respect to their rhythmical changes of caliber, the blood before reaching them having to penetrate the capillary system—are distinctly contractile. This may be clearly seen by examining the larger veins, especially those near the heart, in bats' wings. While, to use Foster's[47] words, "similar rhythmical variations, also possibly due to rhythmical contractions, but possibly also of an entirely passive nature, have been observed, very little is known of any nervous arrangements governing the veins." Granting, for the time being, that veins

[47] Foster: "Text-book of Physiology," 1895.

are not endowed with a vasomotor supply, we find that they nevertheless contract under the influence of suprarenal extract. Szymonowicz[48] observed that the pressure rose and fell in the external jugular vein, along with the pressure caused in the arteries by injections of this substance. Auld,[49] in the course of a series of experiments which had in view the influence of suprarenal extract on the blood, states that when it was injected into a vein "which had been clamped as high up as practicable, on releasing the vein after a few minutes a marked diminution of pressure was recorded as compared with that produced by injection into the free vein." While it is difficult to account for the *general* increase of vascular pressure caused by the extract without including vasomotor nerves in the process, a direct action upon the vascular muscles themselves might underlie the result attained: a question which can only be elucidated by stripping the vessels of all their nervous connections and then watching the effects of the extract. This procedure has been resorted to by Oliver and Schäfer,[50] and these physiologists have shown that a vessel will contract after all the nerves to it are cut. Even a freshly-excised vessel—one, therefore, obviously freed of all nervous influence—will respond to the contracting effects of an aqueous solution of suprarenal extract, and, if a large vessel be used for the experiment to render the change of caliber more appreciable, the diameter will be found reduced nearly one-sixth. Furthermore, these investigators[51] have found that it acts directly on the muscles of the blood-vessels, and that this action occurs equally well *after section of the cord.* As we have seen, destruction of the adrenals or annihilation of their functions is followed by extreme muscular weakness; this normally led them to the conclusion that all varieties of muscle—the striated, non-striated, and the cardiac muscle (which histologically partakes of both kinds of muscular tissue)—are stimulated by the extract. Having further observed that the blood-pressure increased rapidly, giving a steep rise to the kymograph-curve,

[48] Szymonowicz: Archiv für die gesam. Physiol., Bd. lxiv, 1896.
[49] Auld: British Medical Journal, June 3, 1899.
[50] Oliver and Schäfer: Journal of Physiology, vol. xviii, p. 426.
[51] *Ibid.*, p. 230.

they concluded that there had been a strong constriction of the small arteries: strong in their sense, meaning the relative constriction as compared to that of other vessels. This is fully accounted for by the greater relative supply of muscular tissue in these peripheral vessels. As is well known, arteries are endowed with a coat of muscular fibers, which assumes increased thickness and relatively greater mechanical power as the capillaries are approached; so that in the smaller arteries the muscular layer is relatively quite thick. Isaac Ott[52] repeated the test with a Ludwig kymograph and reached the same conclusion.

That all organs are similarly affected owing to their vascular supply was also shown by Oliver and Schäfer by means of the plethysmograph, not alone the limbs, but such organs as the spleen and the kidney being contracted from 20 to 25 per cent. after intravenous injections of the extract. These experiments also showed that great vascular constriction in the splanchnic area was caused. Veins, we have seen, are likewise constricted by suprarenal extract; they also contain muscular fibers in their thinner walls. Although the supply of muscular elements is less important than in the arteries, this is, to a degree, compensated by the greater lumen. That the entire vascular system of the organism is thus acted upon by the suprarenal specific principle, owing to the muscular tissues which it contains, is beyond question.

Can we conclude from these data that the vasomotor system is never influenced by the suprarenal extract, in view of the fact that the blood-pressure is as actively increased by it when the bulb and the cord have been removed or severed? Such a deduction is hardly warranted, since the vasomotor system as a source of stimuli (unlike the inhibitory action referred to, which must obviously withhold stimuli) might, in a normal animal, contribute to the general vascular contraction and perhaps be its main source. Indeed, it is probable that the injected extract does, in an animal deprived of its cord, what it would not do in a normal animal: *i.e.*, find its way into the blood-vessels, owing to the general vascular dilation caused

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[52] Isaac Ott: Medical Bulletin, Jan., 1898.

by the loss of the vasomotor center, and cause contraction of the vascular walls by a direct action upon them. For the time being, therefore, we can only conclude that, *while injections of suprarenal extract may cause cardiac and vascular contraction by directly stimulating the muscular elements of these organs in an animal from which the vasomotor center has been removed, it probably stimulates the vasomotor center in a normal animal.*

Action of the Adrenal Secretion upon the Heart. —We have seen that destruction of the medulla and cord and section of the cardiac nerves in the neck does not prevent the rise of blood-pressure; the vasomotor center being thus functionally eliminated, it is clear that constriction of the vessels does not occur under these conditions, as a result of impulses transmitted through them. Such being the case, it becomes a question whether Oliver and Schäfer's explanation in respect to slowing of the heart by suprarenal extract—namely: that it is due to reflex inhibition of this organ through the constriction of the arterioles induced—still holds. We must not overlook, in this connection, the fact that the active agency through which the heart is slowed, according to their view, is not the suprarenal extract, but the impulses from the center to which the reflex inhibition is attributed, and it is plain that in the absence of this center "inhibition" cannot occur. Hence, as slowing of the heart takes place when this center has been removed, it must be due to some other cause.

Suprarenal extract, if its action is similar to that of the secretion of the adrenals, should, it seems to us, be regarded as a physiological agency, and not be confounded with toxics which pervert normal conditions, nor with elements foreign to existing structures. Considered from this standpoint, the addition of a given proportion of glandular substance to the sum-total of that contained in the organism, or the removal of some by any method, should involve a corresponding augmentation or a diminution of the normal manifestations that represent suprarenal functions, whatever these may be. The injection of suprarenal extract, we have seen, produces a rapid and marked increase of blood-pressure by stimulating the cardiac and vascular *muscles*. When, therefore, we speak of stimulating these structures we imply contraction of the muscular fibers

and approximation of the vascular walls toward the center of the blood-stream. Where is the need of "reflex inhibition," therefore, to account for slowing of the heart's action, when it is combined with increased power of the heart-muscle? The increase of contractile energy normally implicates a slower action in virtue of familiar mechanical principles. As we have seen, the secretion of the adrenals first appears in the suprarenal veins; it must thence flow into the inferior vena cava and penetrate the heart. It seems apparent—to us at least—that we need seek no farther for the source of the slowing of the heart, and that *it is the result of a direct action of the adrenal secretion upon the cardiac muscle.*

Functional Relationship Between Arteries and Their Capillaries Under the Influence of Adrenal Secretion.—The very marked contractile power that suprarenal extract also possesses over the muscular coat of vessels plays an important indirect rôle in the organism which seems to have been overlooked so far: *i.e.*, that, *as capillaries are not supplied with muscles, their walls consisting of endothelial plates, they are not contracted as are arteries and arterioles.*

This embodies two kindred prominent features of pathology: *i.e.*, the fact that *when vessels supplied with a muscular coat contract their capillaries dilate* owing to the increased pressure to which the arterial contraction gives rise within the latter, while the opposite relative mechanism—*when vessels supplied with a muscular coat dilate their capillaries contract*—prevails owing to the resiliency of the latter when the blood in them recedes. In other words, while, in the first case, the blood is crowded outwardly, in the second it is crowded inwardly.

The physiological importance of these propositions will be shown in subsequent chapters, but their bearing and soundness seem sustained by the fact that they alone, of all solutions so far advanced, can satisfactorily explain an experimental phenomenon—a true suprarenal paradox—encountered by Langlois and Charrin in the course of their earlier laboratory work.[53] These observers, in order to study the action of suprarenal substance upon toxic agents and toxins, injected equal

[53] Langlois and Charrin: Comptes-Rendus de la Société de Biologie, July 10, 1896.

doses of virulent cultures into two groups of guinea-pigs, the animals constituting one of the groups having each been deprived of one suprarenal gland. The group of *normal* animals lived altogether 138 hours; that of *mutilated* animals 150 hours. Several experiments of the same kind were performed; invariably did they find that the animals from which one gland had been extirpated lived longer than those left in their normal condition. The differential contractility of vessels and capillaries referred to render this phenomenon a normal consequence under the circumstances: The caliber of the *muscular* vessels, veins, and arteries of the mutilated animals having become enlarged and their walls relaxed by the loss of suprarenal stimulus, engorgement of the larger trunks occurred, and caused *depletion of the remote capillaries,* including those of the bulbar and other neighboring centers. The toxics injected producing their main primary effects upon the latter, and, the quantity of toxic blood transported to them in a given time being smaller than in a normal animal, the longevity of the latter was prolonged in proportion.

We will frequently refer in subsequent chapters to this relative behavior of vessels under the effects of suprarenal secretion or extract; the view, therefore, that *vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation* is only submitted as a postulate for the time being.

VARIATIONS IN THE FUNCTIONAL ACTIVITY OF THE ADRENALS.

Adrenal Insufficiency and its Causes.—Analogy suggests that, besides the normal standard of suprarenal activity, there must be excessive and inadequate activity, both physiological to a certain extent, but pathological when extremes are approached. Hæmorrhage into the adrenals under such conditions would seem, at least, to represent one of the extremes, but which extreme: overactivity or insufficiency? In other words, acute intoxication is attended, we have seen, by an overwhelming increase of blood in the organs, and death seems to follow through cessation of adrenal functions. Is this arrest of action due to the hæmorrhage, or is the hæmorrhage

the result of the impairment by the toxic elements of the functional activity of the organs? If the increase of blood is primary, we would have *overactivity;* if the toxics first paralyze the glandular tissues and hæmorrhage occurs as a result, we would have *insufficiency.*

This question may perhaps be elucidated by tracing to their origin, the symptoms that appear in various cases in which the hæmorrhage occurs as a complication of local chronic disease. These at first seem to afford a ready answer, since the vast majority of them are traceable to organic lesions of the glands that practically annul their efficiency by destroying the greater part of their substance. Partial destruction of the organs and corresponding loss of activity follow each other so logically that any conclusion other than that hæmorrhage occurs as a result of glandular insufficiency seems unwarranted. And yet the opposite might be true, since partial organic destruction of the organs might cause their physiological functions to become concentrated upon what normal structures are left. Both arguments are equally strong, therefore, and furnish but little light. Yet they afford a clue by suggesting the question: *Can* the normal suprarenal substance left assume the additional functional power represented by that lost through destruction of a part of the organ?

While studying the pathological histology of suprarenal hæmorrhage, Arnaud found that it was not in the medulla proper, as generally believed, that these hæmorrhages occurred, but in the tissues of the internal cortical zone. In emphasizing this fact, he states: "It is at this point that the capillaries tear under the influence of a powerful congestion. When the hæmorrhage is important, it is due to rupture of one of the branches of the capsular vein at any point of its walls, and occurs into the medullary substance or into the central conjunctivo-vascular sheath." The medulla proper is thus respected to the last, either a capillary peripheral to it, or some part of the intrinsic portion of the vein—probably weakened by the local disease — constituting the yielding structure. Furthermore, Nature seems to protect the last vestiges of the medullary substance even after a localized hæmorrhage. This is suggested by the fact that Arnaud found in such areas evi-

dent signs of organization, at times indicating a local interstitial inflammatory process, at others a retrogressive metamorphosis recalling that observed in hæmatomata. Finally, using his words: "The normal anatomical elements of the suprarenal gland may be found in a more or less perfect state of integrity, either in the periphery of the growth or at one of its extremities."

This not only typifies the gradual progress of disease in the medullary substance and the steady and certain submission of its structure to the destructive agency, but it also indicates —if we recall the fact that mammals continue to live, as shown by Gourfein, when over nine-tenths of either of their adrenals— that is to say, nineteen-twentieths of both—has been removed —that, unless some compensative action or some accessory organ be present, death occurs when this limit of normal adrenal substance is reached. This is well shown in Andrewes's case, previously alluded to, in which a small strip of normal substance was found post-mortem in the adrenals, the only organs of the body presenting any indication of disease. Again, it becomes evident that Nature supplies mammals with twenty times the amount of medullary substance required under normal circumstances: a proportion probably far exceeded in man, as a result of development incident upon his varied diet. Were the medulla itself capable of assuming compensatory activity, so large a supply for emergencies (the nature of which will be described later on) would hardly have been provided. If analogy be again accepted as guide, other organs do not compensate for what insufficiency organic disease may produce in them by overtaxing remaining normal structures; collateral kindred tissues, supernumerary or accessory organs, vicarious functions, and hypertrophy being all *added* elements, thus constituting either auxiliary resources *per se* or auxiliary resources *plus* compensative growth. Even in the case of the organs of special sense, where the loss of one organ imposes all the physiological labor upon the other, the existing tissues are not overtaxed; they are brought to their highest proficiency by the increase of nutrition which the additional functional use involves. Whatever evidence we have, therefore, tends to show that the *remaining* normal structures of a diseased adrenal do

not assume the physiological functions of the areas destroyed, and it seems clear that the first line of argument—*i.e.*, that hæmorrhage is the result of glandular insufficiency—should prevail.

Further analysis of this question elicits the fact that the symptoms which characterize the progress of the primary organic disease of the adrenals differ totally from those attending the hæmorrhage proper. While the former may hardly cause suffering or be totally obscured by the signs of any concomitant disorder present, the symptoms attending hæmorrhage are particularly violent and sudden, the patient abruptly screaming from excruciatingly intense pain in the abdomen, or dropping at once into apoplectiform coma from which he never rallies. Cerebral apoplexy does not furnish a more vivid picture of the overwhelming effects of hæmorrhage. Yet hæmorrhagic foci in various stages of organization are found at autopsies. Thus, one of Arnaud's cases suddenly fell into apoplectiform coma, and died in 48 hours; the only organs found diseased after death were the adrenals, which contained old hæmatomata, and various more or less organized hæmorrhagic foci which showed that local hæmorrhages into them had repeatedly occurred. The suprarenal substance was entirely destroyed excepting a narrow zone toward the inferior edge of the right organ. The urine, during life, and the kidneys, after death, were found normal. Obviously we cannot well ascribe the acute symptoms to the primary organic lesion, since they appear suddenly, practically without warning, and promptly lead to a fatal issue. Must we, therefore, as in cerebral apoplexy, ascribe them to the hæmorrhage *per se?* Evidently not, since, as we have seen, hæmorrhagic foci of old standing have frequently been found in the organs *post-mortem*, while the acute symptoms had only appeared when death was near. The following conclusions, therefore, seem to conciliate all the data at hand:—

1. The acute symptoms and death which follow hæmorrhage into the adrenals are due to the sudden and complete cessation of adrenal functions.

2. The causes of hæmorrhage into the adrenals are also those of insufficiency of these organs.

Poisons and Variations of the Functional Activity of the Adrenals.—We have only considered so far the hæmorrhages that follow a gradual destruction of the adrenals and which appear only when the fragment of medulla left can no longer fulfill the organ's functions. But there are cases in which, independently of any such a slow destructive local process, the sudden accumulation of one or more toxics suddenly overpowers the adrenals and through the insufficiency thus brought about engender secondary fatal hyperæmia, or hæmorrhage attended with fully as violent symptoms as those observed in Arnaud's case in which sudden death followed a burn of the arm. Andrewes's case, in which death occurred 36 hours after the first symptoms of an acute disease which he thought bore some points of resemblance to hæmorrhagic smallpox, also illustrates this class. In fact, instances such as Andrewes's have so often been noticed by clinicians that Still[54] has proposed a distinct category of cases in which "after an acute illness lasting only two or three days, usually with a purpuric or bullous eruption," death occurs, "and the suprarenal lesion appears to be a part of the fatal issue."

That general intoxication can thus act as an original cause of hæmorrhage has been shown experimentally. Thus, Roger[55] found that inoculation of the guinea-pig with a culture of the pneumobacillus of Friedländer was followed by profuse hæmorrhage into both capsules, the blood actually bursting through the great capsular vein, or causing necrosis of the surrounding elements by mechanical compression. Langlois[56] also demonstrated that suprarenal hæmorrhage could be brought on by the bacillus pyocyaneus. Charrin[57] found that, by injecting diphtheria toxins into guinea-pigs, congestion—which in some instances reached the hæmorrhagic stage—was not alone caused, but he also observed that small doses used repeatedly and during prolonged periods caused hypertrophy of the organs. Petit[58] also noted, after introducing Löffler bacilli in

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[54] Still: Lancet, May 7, 1898.
[55] Roger: Berliner klin. Wochenschrift, Jan. 21, 1894.
[56] Langlois: Le Bulletin Médical, Feb. 7, 1894.
[57] Charrin: La Semaine Médicale, June 3, 1896.
[58] Petit: La Semaine Médicale, June 3, 1895.

fishes in which the suprarenal structure is clearly glandular, that all the phases of excessive reaction could be brought on. Hæmorrhagic foci were found by Wybauw[59] in the adrenals of a child which had died of broncho-pneumonia the result of a tracheotomy for croup. Even drugs may bring on hyperæmia, congestion, and hæmorrhage of the suprarenal glands, as shown by Pilliet,[60] who observed these phenomena after the use of the essence and nitrate of uranium. Essence of cloves has also been found capable of stimulating them to such a degree as to bring on macroscopically-visible lesions.

The next step in our analysis is to ascertain by what process toxic elements can bring on, not hæmorrhage, but the insufficiency of the organs which gives rise to this condition.

The few allusions to this feature in the literature upon suprarenal hæmorrhage refer to this condition as a direct result of various intoxications.

One prominent investigator, for example, writes: "Experiments have shown that certain poisons, essence of cloves, Friedländer's bacillus, diphtheric toxin given by the mouth or by injection to guinea-pigs *produce* acute congestion or hæmorrhage in the suprarenals," thus relegating, with all other writers on the subject, glandular insufficiency to the position of a *consequence* of congestion or hæmorrhage. We, therefore, have no direct data to fall back on for our investigation in this direction.

The view that the suprarenal specific principle itself possesses antitoxic powers, has suggested to those who have accepted it the conclusion that a high degree of toxæmia, by overtaxing the organs, caused congestion, and, if this reached beyond certain limits, hæmorrhage. This conception was mainly based on the view of Brown-Séquard, who was led, by the toxic effects of blood taken from decapsulated animals upon normal ones, to ascribe to the glands themselves a direct antitoxic function. It met with further support in the fact that violent toxæmia invariably follows the removal of both organs, and was therefore accepted by many investigators. It was also

[59] Wybauw: Annales de la Société Royale des Sciences Méd. et Nat. de Belgique, vol. vi, Nos. 2 and 3, 1897.

[60] Pilliet: Le Bulletin Médical, Feb. 7, 1894.

maintained by Dubois,[61] who, having isolated toxic alkaloids from adrenal substance identical in some of their reactions with muscle-toxins, concluded that the adrenals occluded products of organic waste and modified them *in situ*, but that they did not seem to secrete any special substance destined to enter the circulation.

This hypothesis does not seem to us to be able to stand close scrutiny. The destruction of poisons within the adrenals themselves involves the passage of the systemic blood through their cellular elements. When in the cadaver we note the relative dimensions of all the vessels within a narrow radius of the adrenals, it becomes apparent that the conditions are not such as to indicate a provision for the passage of the blood through these organs. The arteries, derived from branches of the phrenic, the renal and often directly from the aorta, are relatively insignificant vessels and totally inadequate to allow the passage through them of enough blood to represent the three hundred and sixty grammes which the cardiac ventricles send into the arteries at each systole, their total sectional area being but a small fraction of that of the aorta, their source of supply. The utter impossibility for the whole volume of blood in the organism to pass through the adrenals in 24 seconds, the length of time required to complete the entire systemic circulation, hardly needs to be emphasized. Again were the blood-stream to traverse the organs, their veins would, to a degree at least, correspond, in diameter, with their arteries. But such is not the case; they are disproportionately large: a fact which in itself shows that the efferent blood must be the carrier of some added product obtained from the glandular structure. It also seems obvious that, if the adrenals were intended to asepticise blood in transit through them, the afferent channels would normally contain blood from all parts of the organism and charged with toxic elements, while the efferent channels would convey the purified blood charged with the suprarenal secretion to the heart, ready for redistribution. Instead of this the afferent vessels receive their blood from the aorta,—arterial blood,—while the efferent vessels pour their

[61] Dubois: Archives de Pathologie norm. et path., vol. viii, 1896.

blood into the vena cava. But, as shown by Alezais and Arnaud[62] in 1890, this blood is *also arterial.* We thus have a short arterial circuit, or loop, which, besides furnishing the adrenals their intrinsic and functional blood-supply, evidently has for its purpose the immediate return to the general circulation of a small quantity of arterial blood charged with what Claude Bernard (1867) has well termed an "internal secretion."

More in keeping with experimentally-established facts are the views which attribute to the secretion itself, when in the blood-stream, the antitoxic functions referred to. Thus, Abelous and Langlois,[63] after a series of careful experiments, reached the conclusion that their normal function was to elaborate an internal secretion capable of neutralizing or destroying the poisonous substances resulting from muscular contractions: a fact further demonstrated to them by the mitigating effects of injected suprarenal extract. More recently these observers[64] amplified their views and concluded that, after removal of both adrenals, there was a true autointoxication, the animals generating poisons which were normally either destroyed or changed in the interior of the glands or by material formed by the organs and poured into the blood. The poisons, they thought, were probably products of muscular activity and also of bacterial origin, and exerted a special influence on the heart and circulatory system. Mosse[65] also believed that the adrenals produced a stimulating substance and that they could simultaneously neutralize poisons formed in various parts of the organism.

Reasoning by analogy, we can surmise that the metabolism of the organs is principally maintained by the passage of blood through them and that the internal secretion represents the physiological product of their metabolism. Under these circumstances, the quantity of blood in them at a given time would stand as the controlling factor, the quantity of active principle secreted into the general circulation being proportionate to this quantity. Have we any ground for the belief

[62] Alezais and Arnaud: Quoted by Arnaud, *loc. cit.*, p. 34.

[63] Abelous and Langlois: Archives de Physiologie norm. et path., vol. iii, p. 267, 1892.

[64] Abelous and Langlois: "Travaux de Laboratoire," Lancet, Aug. 20, 1898.

[65] Mosse: Fortschritte der Medicin, No. 21, 1897.

that the circulation alone may keep up the suprarenal functions? The experiments of Soddu[66] seem to throw light upon this question. In order to ascertain the rôle of the suprarenal peripheral nerves, this investigator isolated the glands of several dogs from their external connections, leaving only the blood-vessels. Although eight animals were submitted to this operation, none died, and all, after a few days, were in their normal health. It is evident that, if the blood alone can thus sustain the life of the organs, an increased flow into them—under, perhaps, the influence of toxic blood upon the centers of their nerve-supply—will involve a corresponding increase of functional activity. That very large or overwhelming doses of any poisonous agency should produce the contrary effect and arrest the functions of the adrenals by annihilating those of their center is suggested by the pathogenesis of suprarenal hæmorrhage.

Still, this involves the existence of an intrinsic nervous supply capable of producing an increased flow of blood into the glands under the stress of an acute toxæmia and a corresponding increase of vascular tension. By suddenly calling the suprarenal functions into violent activity, an excessive dose would thus paralyze them or cause what Arnaud has termed "suprarenal apoplexy": *i.e.*, intrinsic hæmorrhage. To ascertain whether such a nervous influence can exist, and, if it does, whether a poison can stimulate the glands through the latter's nerve-supply, is necessary before further progress can be made.

Biedl[67] studied the effects of various poisons, particularly atropine, to ascertain whether they influenced the character or quantity of suprarenal secretion, and obtained negative results. But can this be said to apply to *all* poisons? A close analysis of this physiologist's work has led us to interpret his experiments in a manner that is not in accord with his conclusion. He states that he found blood-pressure to be increased in the organ by the interruption of artificial respiration. This interruption appears to us to point to an accumulation in the organism of *products of metabolism*, and therefore of poisons of a class which stand out prominently as the basis of phenomena

[66] Soddu: Lo Sperimentale, No. 2, 1898.
[67] Biedl: Pflüger's Archiv, vol. lxvii, H. 9 and 10, 1897.

that promptly end in death. That products of metabolism may with justice be considered as toxic is shown by a detail in Langlois's work, the importance of which does not seem to have attracted sufficient attention: While decapsulated frogs died in 48 hours during summer months, they lived 12 days in the winter: *i.e.*, during hibernation, when metabolic processes are at their lowest ebb. It required a certain ratio of toxic elements to the body-weight to bring on the culminating phenomena; the "fatal dose" was made up in 48 hours, in summer,—*i.e.*, when the full activity and proportionate catabolism prevailed; the same relative dose could only be made up in six times 48 hours when hibernal lethargy reduced tissue-waste in proportion. Thus, Biedl's experiments are not negative in this direction, as he deemed them to be. They appear to us to suggest that, as will be shown in these pages, all toxics do not influence the adrenals with equally marked activity.

Biedl also found that, when the splanchnic nerve was cut and the suprarenal branches were stimulated, hyperæmia appeared in the organs. Howell refers to the striking evidence afforded by the effects of electrical stimulation. If, after cutting the splanchnic nerve and introducing a cannula into the suprarenal vein, the blood is collected and the peripheral end of the cut nerve is stimulated, the quantity of blood obtained in a definite time is not increased, but it is found to contain more of the blood-pressure-raising substance: a fact which indicates that its secretory activity is increased. He therefore concludes that the adrenals act as true glands, and that they are provided with a reflex mechanism corresponding to that of the latter. Biedl also expressed his conviction that secretory fibers as well as vasodilator fibers are present in the splanchnic nerves. Dogiel[68] likewise found that the medullary nerves form complicated plexiform arrangements which terminate upon the surface of the glandular elements; and, furthermore, that the nerve-cells in no way differ from those of any sympathetic ganglion.

All these facts seem to us to warrant the conclusions that:—

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[68] Dogiel: Archiv f. Anatomie und Physiologie, p. 90, 1894.

1. The functions of the adrenals are actively enhanced by stimulation of the splanchnic nerve, and appear to be increased in the same manner by poisons.

2. The functions of the adrenals appear to undergo over-stimulation when a sufficiently active toxic is present in the blood, the result being either hæmorrhage into the adrenals per se, or inhibition of their functions.

MECHANICAL PHENOMENA THAT ATTEND VARIATIONS IN THE FUNCTIONAL ACTIVITY OF THE ADRENALS.

In cases of suprarenal hæmorrhage, as we have seen, two entirely distinct forms of this condition prevail. The first of these occurs when, after a destructive disease, the vestige of medulla left suddenly ceases to secrete enough active principle to continue the physiological functions over which the adrenals preside. The second form is that due to general intoxication.

The symptoms observed in these cases include the following, which may be considered as standard signs: (1) extreme weakness due to gradual decline of muscular power; (2) violent abdominal pain; (3) great reduction of vascular pressure; (4) subnormal temperature; (5) liquid stools; (6) scanty urine or anuria; (7) syncope or convulsions—the whole ending in death in from 20 minutes to 3 days. The sudden annihilation of suprarenal functions obviously involves cessation of secretion. We have seen that the latter maintains the tone of the vascular muscles; the first effect produced, therefore, is suddenly to relax the entire vascular system, as shown by the marked reduction of vascular pressure. As a consequence, the great central trunks—the aorta, the vena cava, etc.—become, by reason of their size and their situation, the main centers of engorgement: an assertion not only demonstrable by clinical signs, but indirectly also by the experiments of Oliver and Schäfer, who found, by plethysmographic observations upon the limbs and spleen, that injections of suprarenal extract produced great vascular constriction chiefly in the splanchnic area. That absence of suprarenal secretion in the organism should produce the opposite result in the same region is obvious.

This central engorgement of suprarenal origin—greatly accentuated through the fact that "vessels supplied with a mus-

cular coat and capillaries are antagonistic in contraction and dilation"—appears to us to be far reaching in its application. Indeed, if the phenomena observed in Asiatic cholera, arsenic poisoning, and other kindred conditions are recalled, the truth of this assertion will appear.

As a result of the central accumulation of blood, the extremities and peripheral tissues, more or less depleted of theirs, are cold; the muscles, also deprived of the greater part of their blood, lose their power; the tension upon the abdominal vessels and neighboring structures, including the unusually rich nervous net-works, produces the intense abdominal pain; engorgement of the intestinal vessels gives rise to copious diarrhœa, which by causing reduction of liquids tends to reduce the renal secretion and sometimes to cause anuria. The depletion of the cerebral vessels accounts for the syncope, and the auto-intoxication, through accumulation of waste-products, for the convulsions. All the symptoms of this terrible disease thus seem to be accounted for—and, we believe, for the first time. They are precisely those that follow removal of both adrenals.

Still, while the various morbid conditions outlined account for the symptoms recorded, closer investigation soon shows that they are only satisfactory as far as they go, and that some features of the symptom-complex are not fully met. Thus, general relaxation of the vascular system means sudden increase of caliber of all vessels, and, therefore, a corresponding increase of area for the blood. Why should it, under these circumstances, accumulate in the larger trunks? Why should it not merely lie dormant in the relaxed vessels evenly distributed throughout them all? Again, gravitation prevails in our body precisely as it does elsewhere. Why should the blood not fill the vessels of the lowest levels of the organism and the back, the nates, the calves, and the heels of the recumbent patient become hypostatically congested, red, and hot, while his toes, knees, abdomen, and face, blanched and cold, reveal by their pallor and coldness the total absence of blood, which has gone to find its level? Instead of this the *entire* surface is frigid and blanched; the lowest portions of the body as well as the uppermost show that all the peripheral capillaries are

depleted and collapsed, the blood in them having been drawn internally: *i.e.*, toward the great abdominal trunks. Again, the intensity of the pain seems to indicate not mere engorgement, but inordinate, disruptive, centrifugal, pressure, for which mere relaxation of the vascular walls cannot account.

On the whole, we are forced to conclude that there must be an overpowering display of centripetal energy from the peripheral capillaries, arterial and venous, as soon as the suprarenal secretion fails to indirectly hold the central vascular walls up to their normal tone. That it is mechanical is suggested by its mode; that it enters into the domain of hydrokinetics is evident; and that loss of the normal equipoise between two forces forms the basis of the process affirms itself on all sides. The solution of the problem suggests itself when we recall, besides the fact that the total sectional area of the capillaries is seven hundred times that of the aorta, the manner in which the capillaries are affected when muscular vessels are dilated. The blood in them, as we have seen, is compressed by the resiliency of their walls and the surrounding tissue, neuroglia, etc., and literally floods the abdominal organs. Indeed, *the peripheral system contains as many sources of pressure as there are capillary tubes in it*—enough many times to account for all the mooted points just reviewed.

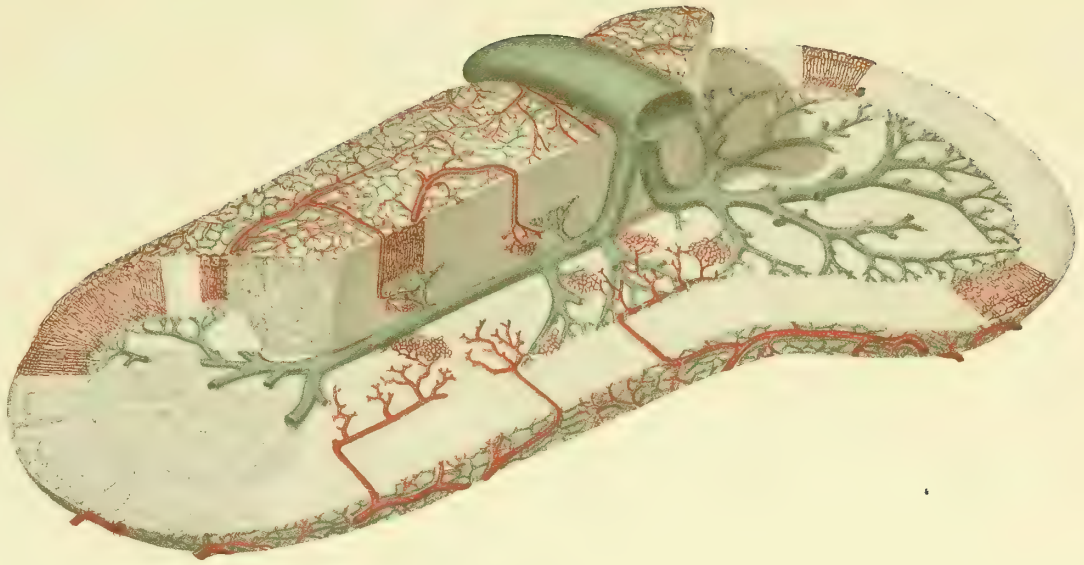
To illustrate the violence of the power exerted in this connection, we may refer to the principle of hydrokinetics,—Pascal's principle,—which underlies the whole mechanical process. This physicist completely filled a strong cask with water, closed it hermetically, then inserted the end of a long, narrow, and close-fitting glass tube through a hole in one of the staves. Into the upper end of the tube, which stood upright, he then slowly poured water. Long before the tube had been filled the cask burst, owing to the excessive pressure within its walls. How was this pressure exercised? "The pressure of a fluid being due to its weight," the pressure in the upper layers of the water in the tube was slight, while that in its lower layers had increased in proportion with its distance from the top, since "pressure at any point in a liquid varies as its depth." "A pressure exerted on a fluid inclosed in a receptacle" being "transmitted undiminished to every part of that receptacle,

and the total pressure exerted on the interior of the latter" being "equal to the area multiplied by the pressure per unit of area," a centrifugal display of force occurred—which far surpassed the resistance of the cask, and it had to yield. The hydraulic press, by means of which the hand of a child can break a steel rail, is based upon this principle.

These principles prevail in the human organism precisely as they do elsewhere in Nature. In the large vascular trunks of the abdomen, abdominal and thoracic viscera, etc., we have closed channels typifying the cask; in the narrow muscular vessels leading to them we have a multitude of conduits portraying the glass tube. Finally, we have the aggregate of pressure of millions of contractile, resilient capillary vessels containing a mass of blood (so great in comparison to the larger vascular structures that these have been considered as subsidiaries to the capillary system) to represent the gobletful of water with which Pascal indirectly caused explosion of his cask. That we have ample power to account for the symptoms mentioned is evident. It also accounts for suprarenal hæmorrhage when violent toxæmia is present. The rich vascular supply of the organs is well shown in the annexed colored plate prepared by J. M. Flint in the course of an exhaustive study of their anatomy, and published in the Johns Hopkins Hospital Reports, two years ago.

Obviously the application of this principle is subject to limitations which the volume of blood accumulated in the vessels of the trunk impose. Admitting, for purposes of illustration, that all the blood of the organism has been forced into the interior of the body, its mass represents a fixed area which the various internal structures must furnish. Thus, while the large vascular trunks bear the brunt of the pressure, all the neighboring organs, including their capillaries, become engorged in proportion as the quantity of blood added to their normal contents is great. In other words, the blood accomdates itself to any room it can find after the larger vascular trunks are engorged, whether it be in a blood-vessel or a viscus. Thus, Boinet,[69] in 45 of his 59 decapsulated rats, found hæm-

[69] Boinet: Gazette des Hôpitaux, July 20, 1899.



CIRCULATION OF THE ADRENALS IN THE DOG. *[J. M. Flint.]*

[Johns Hopkins Hospital Reports.]

orrhage in the lungs in 16, in the spleen in 41, in the thyroid in 13, in the thymus in 11, in the kidneys in 8, in the liver in 5, and in the spinal cord in 5. All this further emphasizes the practical bearing of the postulate: "Vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation."

On the whole, it appears to us that the mechanical phenomena that attend fluctuations of suprarenal functional activity are of surpassing importance in pathology—as will be shown in subsequent chapters. For the present it seems permissible to submit the following conclusions:—

1. Insufficiency of the adrenals is followed by engorgement of the central vascular trunks and depletion of the peripheral capillaries, as indicated by general pallor.

2. Overactivity of the adrenals causes contraction of the central vascular trunks and engorgement of the peripheral capillaries, as indicated by general peripheral hyperæmia, which assumes the stage of "fever" when toxics accumulate in the blood-stream.

THE ADRENALS IN THEIR RELATIONS TO DISEASE AND POISONING.

Effects of Toxins on the Adrenals.—Do poisons of various kinds, venoms, or bacterial toxins cause primary insufficiency by a direct action upon the suprarenal structures or do they cause it indirectly through an influence upon the nervous centers of these organs? We have seen that experimental physiology conclusively shows that the adrenals are provided with a reflex mechanism corresponding to that of true glands, and that electrical stimulation of the suprarenal branch of the splanchnic nerve can cause increase of secretory activity. These facts, considered simultaneously, suggest that the presence of an unusual proportion of toxic elements in the blood may, physiologically, so affect the nervous centers of the adrenals as to increase the functional activity of the latter. On the other hand, ample *post-mortem* evidence is available to show that tubercular, cancerous, and other morbid processes may find in the organs a soil of activity. It is evident, therefore, that their structure is vulnerable from both directions: *i.e.*, that disease, poisons, etc., can assail them indirectly

through their nervous supply, and directly by invasion of pathogenic elements of various kinds.

What is the nature of the pathological process that follows infection or the ingestion of poisons? The relation between the class of cases previously described and this is well shown by the reports of several observers, who not only refer to the invariable presence of hyperæmia, but also to local hæmorrhagic processes. René Wybauw, for example,[70] injected diphtheria toxin into the peritoneal cavity of a large number of guinea-pigs, causing death within three days. In all these animals the adrenals had become somewhat enlarged and showed intense hyperæmia, the central vein being particularly engorged. In one of them, a guinea-pig, the disease followed an acute course; the vascular epithelium had yielded to the pressure and the organs showed abundant hæmorrhages. The reticular and medullary zones, in which capillaries are especially abundant, presented the most marked lesions.

We have already seen that Abelous and Langlois also found that the injection of various bacterial cultures caused vascular lesions varying from slight congestion to severe hæmorrhage. Two cases, reported by different observers, are particularly interesting in this connection: In the one, a case of acute toxæmia reported by Andrewes,[71] death occurred in 36 hours, and the adrenals alone showed lesions—interstitial hæmorrhage. In the other, reported by W. S. Colman,[72] the symptoms also indicated a general infection; death occurred in about 25 hours, and no lesion other than suprarenal interstitial hæmorrhage was found. The interesting feature of these cases, however, is that both observers submitted blood taken from the hæmorrhagic foci in the organs to bacteriological examination. Andrewes invariably obtained sterile cultures, and he states that, if any organisms were present, "there were none that grew upon ordinary media or stained with ordinary reagents." Colman not only reached the same result with blood from the adrenals proper, but with blood taken from

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[70] René Wybauw: Annales de la Société Royale des Sciences Méd. et Nat. de Bruxelles, vol. vi, p. 134, Nos. 2 and 3, 1897.

[71] Andrewes: Lancet, May 7, 1898.

[72] W. S. Colman: Lancet, May 7, 1898.

other organs. The cases had doubtless been caused by a specific toxin, but with the ever-present hyperæmia as a terminal feature.

Does a specific organism or its toxin produce its own characteristic lesion in the adrenals? Wybauw[73] states that he has invariably found in these organs, after the injection of diphtheric toxins in rabbits, the histological lesions found elsewhere in this disease. He further noted that the point of union of the reticular and medullary zones, where the capillaries are especially numerous, presented the well-known type of degeneration, while the slides also clearly showed all the stages of cellular destruction, with more or less disintegration of the nuclei. The latter were also undergoing retrogressive stages, gradual loss of regular outline, irregular perimetric retraction, etc. He likewise examined microscopically the adrenals of a guinea-pig killed with cholera germs, but in this connection he says: "The adrenals are the seat of much less pronounced changes than those of the diphtheric guinea-pig. They are redder than normal. But the examination shows lesions which *must certainly be produced by the same mechanism.* The cells are irregular, the nucleus having lost in places its characteristic structure," etc. In a case of broncho-pneumonia following tracheotomy for diphtheria, he was able to note the same changes that he had observed in the diphtheric rabbits and choleraic guinea-pigs, but less marked, the patient having died of the concomitant disease before the diphtheric process had become far advanced. Arnaud,[74] in a case of suprarenal hæmorrhage associated with liver-abscess, also found lesions in the suprarenal medulla characterized by cellular degeneration, granular disintegration, etc.: *i.e.*, a general necrobiosis of septic origin. If to these results we add those of Andrewes and Colman, referred to above, it seems clear that we can, with Wybauw, conclude that bacterial toxins as a class possess a direct destructive action upon adrenal tissue.

But this observer ascribes to the adrenals a special sensitiveness to the influence of diphtheric toxins. While this may be the case, it seems to us that, inasmuch as a specific toxin

[73] Wybauw: *Loc. cit.*, pp. 134 and 165.
[74] Arnaud: *Loc. cit.*, p. 15.

does not produce a characteristic lesion in them, the phenomena witnessed, histological and symptomatic, should rather be considered as expressions of excessive stimulation or exhaustion of these organs. The various toxins differ in potency precisely as do other poisons; why their mode of action should differ would be difficult to show. On the other hand, it may easily be demonstrated that all poisons affect the adrenals in a similar way, and in proportion to their virulence and dose. In curare poisoning, for example, the symptoms produced so exactly portray those that follow extirpation of both organs in mammals that Abelous and Langlois[75] were led to conclude that there were in the blood various substances possibly originating in the chemical changes of muscular contraction, which produced curare-like symptoms, and which were destroyed or neutralized by the internal secretion of the adrenals. Tillie,[76] after a series of experiments (which did not refer to the adrenals), thus describes the physiological effects of curare: "With larger doses there is *dilation of the abdominal vessels*,[77] and, hence, accumulation of blood, little or nothing of this fluid entering the empty ventricle notwithstanding that the heart may continue to beat. Curarine causes an almost immediate fall of blood-pressure in mammals; it occurs even after section of the vagi, after a paralyzing dose of atropine, after division of all the cardiac nerves, after section of the spinal cord, and after paralysis of the central reflexes by urethane. The cause, therefore, of the fall of pressure must be due to a direct action upon the peripheral nerves or upon the muscles of the blood-vessel walls." Probably stronger evidence to show the direct paralyzing action of curare upon the adrenals could not be found.

The common action of various toxins may be as clearly demonstrated. Thus, Langlois and Charrin[78] invariably noted hypertrophy of the suprarenal tissues after the prolonged use of diphtheric toxins in small quantities, in guinea-pigs. In one of the animals the organs had increased to over four times

[75] Abelous and Langlois: Archives de Physiologie norm. et path., vol. xiii, p. 267.

[76] Tillie: Medical Chronicle, March, 1891.

[77] The italics are our own.

[78] Langlois and Charrin: La Médecine Moderne, Feb. 5, 1896.

their normal size. The same phenomena followed injections of bacillus pyocyaneus. Petit[79] also found hypertrophy to follow filtered cultures of the Löffler bacillus in fishes. That the hypertrophic process is compensative is shown by the fact that hypertrophy also occurs in the remaining gland when one has been extirpated. Stilling[80] observed that in young rabbits the remaining adrenal sometimes attained very large size; Auld[81] also reported several instances in cats. In the presence of these facts it is evident that the adrenals are submitted to excessive activity when toxics are introduced into the organism, and that the local lesions are the expression of a physiological function utilized beyond its normal limits. The histological lesions found post-mortem are no longer pathological manifestations of the toxins introduced; they are those of overuse and common to all.

That we are dealing with the effects of overactivity is sustained by evidence from another direction. In the instances in which hypertrophy was caused by injections of toxins these were administered in small doses at frequent intervals, the process extending over a period of many weeks. If we analyze Wybauw's report, there are points which tend to indicate even more than the direct effects of toxins noted. This author refers to promiscuously-distributed swollen cells, the protoplasm of which is less clear than usual, and to other features that recall the characteristics of cloudy swelling observed most frequently in the liver and kidney and in the heart-muscle. This we know may be caused not only by bacterial toxins, but also, and with equal frequency, by nutritional disturbances excited by nervous stimulation. We have evidence that the excessive stimulation of the nervous center of the organs must underlie the overactivity induced, in the fact that electrical stimulation of the splanchnic nerve causes, as we have seen, an increase of suprarenal secretion.

Of course, both processes—local lesions induced directly by the toxins and those brought on through excessive functional activity—may be simultaneously present in the organs.

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[79] Petit: *Loc. cit.*

[80] Stilling: Virchow's Archiv, Dec., 1889.

[81] Auld: British Medical Journal, June 3, 1899.

Thus, advanced nuclear degeneration is rarely seen in cloudy swelling, while in Wybauw's preparations it is marked, indicating the destructive effects. It seems clear, therefore, that we thus have simultaneously pictured, not only the direct effects of the poison, but also the primary effects of excessive activity, the physiological "spontaneous wearing out of living parts" of Virchow having become pathological.

Cloudy swelling and its almost unfailing sequel, fatty degeneration, represent the dominant processes, however: a statement which suggests that the latter should show itself even more frequently in the adrenals than elsewhere, in consideration of the fact that agencies capable of inducing this pathogenic overactivity not only include poisons, but also a large number of diseases, particularly those of childhood. Arnaud,[82] alluding to the evidences of fatty degeneration in the adrenals observed *post-mortem*, writes: "This lesion, which is appreciable only by histological examination, is very common, as shown by my personal researches. It existed to a more or less marked extent 36 times in 100 subjects whose adrenals had been collected *at random* at autopsies." Rolleston[83] refers to this subject in the following words: "In the suprarenal bodies of adults fatty change is so common as to be a physiological condition. The fat occurs as large globules in the cells. This change may be present throughout the whole of the cortex or be best marked in the zona fasciculata. The medulla is occasionally seen to be occupied by fat, but never to the same extent as the cortex, while in children there is little fat normally. Attlee found, however, some, though slight, fatty change in still-born children. In children dying from marasmus there was marked fatty change, which was more frequent than in the liver. The cortex was affected in all, and the medulla in 6 out of the 9. *Experimentally he found that starvation, suppuration, or poisoning, whether acute or chronic, gave rise to fatty changes*"[84]: further evidence that all intoxications exercise the brunt of their action upon these organs. And yet Rolleston but voices the present conception of the position

[82] Arnaud: *Loc. cit.*, p. 6.
[83] Rolleston: Allbutt's "Practice," p. 567.
[84] The italics are our own.

occupied by the adrenals in pathology when he adds: "Fatty change does not give rise to any symptoms."

If the views herein recorded are not erroneous, it would seem far more exact to state that *fatty change of the adrenals represents an end-result of almost all morbid processes attended with the introduction into the blood of a toxic, whether this be a vegetable or mineral poison, a toxin, a catabolic product, a venom, etc.*, any agency in fact, extrinsic or intrinsic, capable of inducing what we now term a "toxæmia." Another deduction which logically suggests itself is that all the major symptoms now ascribed to the direct action of all these toxics are primarily ascribable to their morbid effects upon the adrenals, either directly upon the organs themselves or indirectly upon them through a primary action upon the centers of their nervous supply. In other words, it would appear that *all major symptoms witnessed in diseases in which the blood is invaded by a poison are in reality manifestations of overactivity, insufficiency, or total inactivity of the adrenals.*

The latter conclusion, however, imposes as conditions that all poisons give rise to similar symptoms, due allowance being made for the differences in power as represented by the activity of an agent plus the dose administered, and that these symptoms precisely coincide with those of suprarenal insufficiency or those which follow removal of both adrenals. That such is the case is shown below.

Effects of Venoms, Vegetable and Mineral Poisons on the Adrenals.—Removal of both organs, as we have seen, is followed by extreme muscular weakness, marked reduction of blood-pressure, hypothermia, dyspnœa, and blood-changes. All these phenomena should appear under the influence of sufficiently active poisons if the above conclusion is warranted.

To strengthen the evidence adduced only works will be used for comparison in which the observations given in no way refer to the suprarenal glands. For the study of venoms we are fortunate in having at our disposal a comprehensive and admirable article by J. Noé,[85] of Paris, which gives a complete retrospect of all the main investigations upon this subject dur-

[85] J. Noé: Archives Générales de Médecine, Jan., Feb., Sept., and Nov., 1899.

ing the last fifty years, and in which the semeiological and pathological effects of the various venoms, ranging from those of insects to those of reptiles, are studied. For the study of the toxic manifestations of drugs the excellent work on "Therapeutics," by Horatio C. Wood,[86] of Philadelphia, will be utilized. The agents to be analyzed in this connection will not be selected, however, among any special class—cardiac depressants, depresso-motors, antipyretics, and the like to facilitate our task; they will be taken in the promiscuous order afforded by the index, in which the first letter of the name given each drug is the only feature involving sequence. Obviously only those subjects in which the cardinal symptoms referred to—muscular weakness, variations of vascular pressure and temperature, etc.—have been sufficiently studied by the author will be considered. This includes a large proportion of the best-known drugs, and may with all fairness be accepted as representatives of all those capable of giving rise to toxic symptoms.

Muscular Weakness.—The great muscular weakness attending insufficiency of the adrenals, as shown in Addison's disease and so marked after removal of both organs, finds its counterpart in the symptomatology of intoxication as well with venoms as with vegetable and mineral poisons. Vulpian in 1869 called attention to the progressive asthenia, followed by somnolence with motor phenomena recalling those of curare poisoning, caused by cobra-venom. Paul Bert noted that muscular activity disappeared after scorpion toxæmia, and that the muscles failed to respond to strong induction currents. He also observed that even bee-venom caused loss of motor activity, and therefore concluded that this toxic acted on the muscular system. Salamandrine was likewise found to cause progressive weakness, the voluntary and spasmodic movements, *particularly those of the hind-quarters*, being abolished. Phisalix and Bertrand also observed that the main effect of toad-venom was paralysis of the lower extremities. Norris Wolfenden ascertained that cobra-venom caused ascending paralysis, but that this varied according to the species in which it occurred; in

[86] Wood: "Therapeutics," eleventh edition, 1900.

man paraplegia was produced, while all four extremities were finally paralyzed in animals. Finally, Valentin[87] noted that eel-venom, ichthyotoxin, caused absolute loss of conductivity of sensation in the lower extremities.

Acetanilid is stated by Bókay[88] to "paralyze motor nerve-endings of the frogs' muscles in a manner similar to curare. . . . In the poisoned animal just before death the muscles respond actively": evidence that the muscular elements themselves were not affected by the poison, and that the "tonus," of which suprarenal secretion is the recognized source, alone failed them. Aconite is said by Wood to give rise in therapeutic doses to "a sense of muscular inertia and weakness," and if the dose administered be larger "the muscular weakness is extreme." Alcoholic muscular relaxation hardly needs to be insisted upon; the attitudes of drunkards speak for themselves. Antimony in large doses is referred to as causing great muscular relaxation, the exhaustion becoming extreme after toxic doses. Antipyrin acts according to the dose administered, causing rigidity in large doses (excessive momentary suprarenal tonus), while "in overwhelming amount," according to Blumeneau,[89] it causes in frogs "muscular relaxation with loss of reflex activity deepening into complete paralysis and death." Arsenic causes, even in small doses in the frog, cessation of voluntary movement. The muscular weakness, lapsing into complete exhaustion, that follows arsenic poisoning, is a familiar clinical picture.

Belladonna—*i.e.*, its alkaloid, atropine—is referred to as follows: "When an enormous dose of the alkaloid has been taken, a fatal stupor, with muscular relaxation, may develop at once. . . . Probably, however, in all cases stupor and muscular paralysis finally develop." . . . Bromism, according to E. H. Clarke, is attended with "muscular weakness which becomes paralysis." Camphor is referred to as giving rise in large doses to a feeling of lassitude, while general paralysis follows the ingestion of poisonous doses. Carbolic acid is stated by Wood to give rise to muscular weakness, but a striking indi-

[87] Valentin: Zeitschrift für Biologie, 1877.
[88] Bókay: Deutsche med. Wochenschrift, Oct., 1897.
[89] Blumeneau: St. Petersburger med. Wochenschrift, 1887.

cation of the relationship between the effects of carbolic-acid poisoning and disturbed suprarenal functions is the reference to the fact that in frogs and mammals "the paralyzing influences of carbolic acid are usually first manifested upon the hind-legs." . . . Chloral is referred to as producing muscular weakness and then paralysis. Labbée is stated to have found that after death the muscles respond perfectly to galvanism, thus eliminating organic alteration of the muscular tissues as a factor in the paralytic phenomena.

The muscular relaxation witnessed in chloroform anæsthesia needs only to be recalled. Cocaine is termed by Wood "a muscle-poison, stimulating and afterward depressing the functional activity." Copper is referred to as capable of causing progressive paralysis. Bókay[90] found that the muscles were affected very early by *continuous* doses, "cloudiness of their protoplasm and disappearance of their cross-striation coming on." This recalls the cloudy swelling previously referred to as observed even in the adrenals themselves, the precursor of fatty degeneration. Digitalis in toxic doses is said to cause lassitude, prostration, and muscular tremors. Ether anæsthesia, and the profound muscular relaxation produced, need only be mentioned. Hydrocyanic acid is termed a "paralyzant to the muscles," general paralysis ensuing almost immediately after taking a toxic dose. That the hind-extremities are first paralyzed in animals we have ascertained. The effects of mercury in this connection are well known,—"mercurial palsy," which occurs within a few hours after the poison enters the organism; the "peculiar *brownish* hue of the whole body" . . . "which generally accompanies the disease," are easily accounted for with suprarenal insufficiency as an element of the process.

Opium was found as long ago as 1826 by Charvet[91] to cause "progressive loss of power in the contractile tissue, ending in death; in fishes, paralysis and convulsions; in birds and mammals, paralysis, convulsions, and stupor." Interesting in this connection is the observation credited to Albers[92] that "convulsive movements occur in limbs after section of their

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[90] Bókay: Pester med.-chir. Presse, 33, 1897.
[91] Charvet: Pereira's "Materia Medica," 1035; Philadelphia, 1854.
[92] Albers: Virchow's Archiv, xxvi, 229.

nerves." In man "alarming depression" also occurs. Oxalic-acid poisoning is stated to be attended with "entire prostration of strength." Phosphorus poisoning also produces "a sense of weakness and general wretchedness." Physostigma gives rise, after the full therapeutic dose, to "slight weakness and dislike for muscular exertion" and in large doses to "great muscular weakness." "When an animal receives a small fatal dose of Calabar bean, after a time muscular tremors appear, and almost immediately the victim falls to the ground or lies down in a state of perfect muscular flaccidity." Santonin poisoning is attended with trembling, which increases in severity until convulsions occur.

Silver was observed by Charcot and Ball[93] to cause, when injected directly into the blood, sudden paralysis of the hind-extremities. Strychnine in large doses produces "muscular twitchings and startings and formications" while toxic doses induce spasm, opisthotonos, etc. Muscular relaxation other than that occurring between convulsions is not referred to, though death during these periods of exhaustion are stated to sometimes occur. Asphyxia caused by the "unyielding, spasmodically-contracted muscles" doubtless occurs before the stage of suprarenal insufficiency is reached, strychnine, of all agents, standing prominently as the most active suprarenal stimulant. Tobacco poisoning is stated to cause "absolute loss of muscular strength" and finally complete collapse. Veratrine is referred to as primarily a muscle-poison, a stage of hyper-excitability preceding the stage of paralysis. Zinc poisoning is attended with prostration. As to chronic poisoning by this metal, Wood refers to the experiments of Sacher,[94] who found that intravenous injections of very large doses of zinc salts produced paralysis of the voluntary muscles.

We thus have typified in all these various poisonous agents not only the typical muscular weakness observed in recognized diseases of the adrenals and the total prostration following removal of the organs, but we can also discern in the list a series of grades or degrees in the loss of muscular function ranging

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[93] Charcot and Ball: Gazette Médicale, 1864.
[94] Sacher: Thesis, Dorpat, 1893.

from slight weakness to total paralysis. We not only behold total loss of muscular power, therefore, as a result of suprarenal-extract poisoning, but also as the result of absence of secretion: *i.e.*, of advanced suprarenal insufficiency. And what is more simple than this cause of paralysis: the mere loss of tone afforded by absence of secretion? That all remedies sufficiently active to induce the phenomena outlined give rise to both these phases of muscular activity through a primary effect upon the adrenals—the source of the twitchings ascribed to strychnine, for instance—will again be referred to.

Vascular Pressure. — The marked decrease of vascular pressure accompanied by the still more evident cardiac weakness which attends loss of suprarenal function has been emphasized. We have also seen that the injection of suprarenal extract into the circulation, besides enhancing vascular tone, slows the heart. Both these phenomena appear under the influence of venoms and poisons. In small doses these tend to increase vascular pressure and slow the heart; in powerful doses they reduce vascular pressure and weaken the heart.

Kauffmann is referred to by Noé as having observed that viper-venom at once causes enormous reduction of arterial pressure. "It is especially marked in the digestive tract," says this author, "a true gastro-intestinal apoplexy; it is the main cause of death." Phisalix, on the other hand, observed that viper-venom caused general vasodilation, congestion of all organs, rapid lowering of blood-pressure, and weak pulse; and found the blood to contain but a small amount of CO_2. Couty also observed vasodilation after injections of rattlesnake-poison. Overactivity of the adrenals, typified by Swale Vincent's injections into animals, and which caused hæmaturia, nose-bleed, etc., soon followed by symptoms of marked insufficiency, is well illustrated by Fraser, who states that hæmorrhages are most marked in viper and rattlesnake intoxication, and that hæmaturia and hæmoglobinuria were caused when the full dose of venom has not entered the wound. Hæmaturia attends, we shall see, overactivity; hæmoglobinuria, insufficiency. Fayrer observed that viper-venom caused intense hæmorrhage and hæmaturia. Calmette also associates this symptom with the cobra-venom. Scorpion-venom, according to

Paul Bert, Phisalix, de Varigny, and others, sometimes gives rise to intense congestion of certain viscera.

Are we really dealing, in this connection, with variations of vascular tension and pressure? The presence of *increased* vascular pressure is illustrated by the effects of smaller doses or weaker poisons. Thus, Phisalix and Langlois[95] are stated to have found that salamandrine in small doses stimulated cardiac action and greatly increased vascular pressure in dogs, while large doses gave rise to ecchymotic spots and hæmorrhages. So intense was the central depletion observed in frogs that Dutartre hardly found a few drops of blood in the heart. Mosso found that ichthyotoxin, the tissue-venom of the eel, greatly increased blood-pressure, causing convulsions, while small doses only caused slight and ephemeral increase of pressure, followed by a tendency toward diminution. He further ascertained manometrically that the venom did not paralyze the vessels (obviously since the poison had nothing to do with it): a fact also sustained by the regular contractions of the rabbit's auricles.

Intimately associated with the phenomena just outlined are those connected with the heart. Do venoms affect this organ as does adrenal extract? Weir Mitchell and Reichert observed that snake-venom exercised a moderating action on the heart. We now know that suprarenal extract acts directly on the muscular elements of this organ. Vulpian called attention to the fact that toad-venom and triton-venom arrested the heart by reducing the irritability of its walls. Kauffmann found that viper-venom caused it to beat rapidly, but feebly, the weakness increasing with the rapidity of the beats, *but he could find no moderator nerves.* A weaker venom, on the other hand, salamandrine, in small doses, was found by Phisalix and Langlois[96] to strengthen the weakened animal's heart and its arterial tension. The correspondence between these effects and those induced by suprarenal extract is thus further emphasized, since in all the venoms both actions are observable according to the dose and the power brought into activity.

The same variations of pressure, cardiac and vascular, are

[95] Phisalix and Langlois: Académie des Sciences, Sept. 6, 1899.
[96] *Ibid.*, Sept. 16, 1899.

observed in connection with poisons. Acetanilid in toxic doses rapidly produces insufficiency. Even in repeated doses, according to Wood, it may cause a peculiar cyanotic condition of the face and extremities, while "the fall of temperature is accompanied by profuse sweating." . . . "In rare cases," says the author, "the lowering of the bodily temperature has been coincident with the occurrence of collapse." The transition from overactivity to insufficiency would thus seem to occur at the onset of hypothermia, deficiency of suprarenal secretion being indicated by the diastolic heart found after death from collapse. The sweating must obviously be due to the loss of tone of the muscles of the sweat-glands. In aconite we first have the characteristic picture of injections of suprarenal extract indicating suprarenal activity, followed by the characteristic signs of insufficiency. "In frogs," writes Wood, "the phenomena caused by aconite are similar to those seen in man, and consist of, at first, a reduction and afterward an increase in the rate of the heart's beat, with a loss of power in the circulation, and finally irregular systolic movements, with marked prolonged diastolic pauses ending in diastolic arrest." Alcohol is referred to as acting upon the heart as a stimulant in small doses and as causing marked increase of arterial pressure. A large dose, on the other hand, is followed by a fall of arterial pressure and acts as a depressant and paralyzant. The stimulation is doubtless exercised upon the suprarenal glands, and the reaction stage marks the onset of insufficiency whose manifestations progress as more alcohol is imbibed. Antimony is another agent which, like acetanilid, seems rapidly to induce suprarenal insufficiency. "In the lower animals," writes Wood, "all doses of antimony sufficient to cause any apparent effect progressively lower the arterial pressure; the pulse is sometimes at first temporarily accelerated, but usually the slowing of the pulse occurs from the beginning of the poisoning. During this period of slow pulse the diastolic pauses are extremely long and the pulse-waves greatly augmented, it may be to five times their original size. After a time the pulse usually becomes very rapid, the pulse-waves very small, the arterial pressure almost extinguished, and in a few minutes diastolic arrest occurs." The process referred to in these remarks,

based on the experiments of Ackermann[97] and Ernst Sentz,[98] underlies the clinical phenomena familiar to all as well as those of Asiatic cholera, cholera infantum, and cholera morbus.

Antipyrin resembles acetanilid in its action. "Demme, Arduin, Armand, H. Casimir,[99] and Cerna and Carter[100] have separately determined by experiment that in moderate doses antipyrin increases the arterial pressure, while toxic doses lower the pressure." "The toxic dose of arsenic," says Professor Wood, "greatly lessens the rate and force of the pulse-beat and markedly lowers the blood-pressure." He refers to the experiments of Unterberger,[101] who "found that in an animal under the influence of the poison neither galvanization of a sensory nerve nor of the vasomotor center in the upper cord had any influence upon the force of the blood-current." The reason for this is apparent with the adrenal secretion as a factor of the process. Belladonna, or, better, its alkaloid, atropine, it is stated, "may cause a primary slowing of the pulse (very brief and only to be occasionally demonstrated), followed by an extraordinarily rapid pulse, with a very great rise in the arterial pressure; followed, after a time, if the dose has been sufficient, by a progressive lowering of pressure until death is reached, the rapidity of the pulse being maintained until the end" . . . "in atropinized animals neither section nor galvanization of the vagi affects the pulse-rate."

Bromides, these apparently benign agents, stand in this connection as actively toxic as many of the more virulent drugs reviewed. They seem to inhibit suprarenal activity even in small doses. Schouten[102] found that, during the injection of a 2-per-cent. solution into the vena cava of a rabbit, "the cardiac systole grew slower, the diastolic pauses longer, and finally the heart stood still." Wood considers it as "well established that large, toxic doses of the bromides exert a direct paralyzing action on the heart, lessening both the force and the frequency of the beat, and finally causing diastolic arrest." The relation

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[97] Ackermann: Virchow's Archiv, xxv, 531.
[98] Ernst Sentz: Inaugural Dissertation, Dorpat, 1853.
[99] H. Casimir: Thèse de Lyon, 1886.
[100] Cerna and Carter: "New Remedies," 1892.
[101] Unterberger: Archiv für exp. Path., etc., ii.
[102] Schouten: Archiv für Heilkunde, xii, 97, 1871.

between the suprarenal insufficiency induced and the arrest of the heart is apparent. Camphor is referred to as acting directly as a stimulant to the heart-muscle. Interesting, however, is Professor Wood's reference to the contrary results reached by Alexander Lewin,[103] which he ascribes to "the use of overwhelming doses, camphor first stimulating and then depressing the heart-muscle." Carbolic acid he refers to in the following words: "The prominent symptoms induced by lethal doses are disturbance of respiration; stupor, deepening into coma; rapid, feeble pulse; muscular weakness; abolished reflexes; collapse; fall of temperature, and albuminous or bloody urine, etc." It is perhaps necessary to point to these phenomena as the exact counterpart of total suprarenal insufficiency. Chloral at first causes slowing of the heart's action. "Very large doses," according to both Andrews and Da Costa,[104] "decidedly lessen arterial pressure. The characteristic influence of therapeutic, and still more of toxic, doses is to produce a fall in the blood-pressure, usually accompanied by a lessening in the frequency of the heart's action."

The preliminary stimulation of cardiac action induced by chloroform is well known. "Putting all the evidence together," writes Wood, "it seems to us to have been completely demonstrated by physiologists, first, that chloroform is a direct depressant and paralyzant to the heart-muscle or its contained ganglia; second, that the fall of blood-pressure which occurs in chloroformization is in great part due to this direct depression of the heart." Cocaine, as shown by various investigators, produces an increase of arterial pressure when given in moderate doses. "The drift of the present evidence," says Wood, "is to show that the small dose of cocaine moderately stimulates the heart, and that the large, toxic dose finally depresses it."

Copper is another agent the clinical phenomena of which recall those of cholera: toxic doses paralyze the heart in lower animals. Digitalis, in batrachians, raises blood-pressure and depresses it in the last stage. "In most of the experiments of

[103] Alexander Lewin: Archiv für exp. Path., etc., 1890.

[104] Andrews and Da Costa: American Journal of the Medical Sciences, April, 1870.

J. P. Arnold and H. C. Wood, Jr., upon dogs," writes Wood, "the change from a slow to a rapid pulse has been abrupt and usually accompanied by an enormous rise of the already elevated blood-pressure. At the end, the fall of pressure is very sudden and rapid, so that it has immediately preceded death." . . . "It seems to be clearly established that in poisoning of the mammal by digitalis the heart is arrested, not in systole, but in diastole." It also seems "very certain that the proposition framed for the lower mammals applies also to man."

Ether is referred to in the following terms: "Our present evidences show that there is, during ether anæsthesia, a rise of pressure, which is, at least in part, the result of cardiac action. . . . This rise is followed by a fall." . . . Hydrocyanic acid is probably the most violent suprarenal paralyzant; it was found by Preyer, Lecorché, and Meuriot to produce, in sufficient amount and concentration, instantaneous diastolic arrest. In large, though not enormous, doses Preyer and Laschkewitsch noted that "it first produced a sudden prolonged arrest of the heart, followed by an augmentation in the rapidity of the cardiac action, and after this a diminution of the rate: to the normal number in cases of recovery, to cardiac standstill in cases of death." Small, non-toxic doses simply slow the heart's action.

Mercury, in the form of corrosive sublimate, also gives rise to choleraic symptoms in toxic doses. "In the course of two or three hours," says Wood, "very rarely in less than an hour, collapse occurs, with small, frequent, irregular pulse." Opium is referred to as follows: "In man the circulatory phenomena are a slight primary evanescent acceleration of the pulse-rate (Nothnagel[105]), succeeded by the characteristic slowing and increased fullness and force of the pulse, which is followed by a return to the normal pulse or a great increase of the rapidity and loss of strength during the third stage." . Experimentally it was found to cause arrest of the heart in diastole. Oxalic-acid poisoning is also attended by a small, irregular pulse. Phosphorus, in the very acute cases of poisoning, may be at-

[105] Nothnagel: "Handb. d. Arzeneimittellehre," 1870.

tended with pronounced cardiac weakness, even in the primary stage. "The patient," says Wood, "may suddenly succumb to collapse and cardiac paralysis." Physostigma, injected in poisonous doses into the jugular vein, causes death from syncope or from simultaneous "failure of the cardiac and respiratory functions, and the heart is arrested in diastole. When smaller doses are exhibited, there is slowing of the heart's action." Santonin in toxic doses causes slowing of the pulse in dogs, and rapid or slow, feeble pulse in children. Silver salts when injected into the veins were found by Charcot and Ball, Rabuteau and Mourier to cause instantaneous death, which is ascribed by these investigators to "a direct paralyzing influence of the drug upon the muscle of the heart." Strychnine is stated by Wood to produce in full dose "a rise of the arterial pressure, which is enormously increased during the convulsion, after which there is a very pronounced fall in the arterial pressure." Tobacco, or rather its alkaloid, nicotine, is referred to as having "a very distinct influence" upon the circulation, "producing, first, rise, and afterward fall, of pressure." Veratrine, even in small doses, causes slowing and weakening of the pulse, and a toxic dose has produced collapse, with rapid, thready, and irregular pulse. The toxic effects of zinc are similar to those of copper referred to above.

This long list of toxics can be said to fully indicate, first, that all poisons primarily induce a more or less marked period of overactivity: *i.e.*, increased vascular pressure and cardiac energy. The central vascular trunks are suddenly contracted, the heart is stimulated by the direct action of an unusual amount of suprarenal secretion. Second, that at a given time and when the dose and power of the toxic are sufficiently great, this increase of activity ceases and is replaced by a more or less marked decrease of vascular pressure and cardiac energy. The central vascular trunks are then dilated and the heart-action reduced through a corresponding reduction of suprarenal secretion.

Temperature. — A marked reduction in the temperature, we have seen, is a prominent symptom of advanced suprarenal insufficiency. The symptomatology of all forms of poisoning also includes this phenomenon. As to venoms,

Phisalix[106] refers to hypothermia as the most marked characteristic of viper intoxication. He found it to occur rapidly and to an intense degree, reaching in guinea-pigs as low as 22° C., though death usually occurred at 32° C. He also observed that hypothermia prevailed after injections of ichthyotoxin, or eel-venom, while Bottard[107] noted it in guinea-pigs after injections of sea-dragon venom. Hutinel also observed it in a case of cobra-bite, the temperature of the patient, a man, reaching down to 31.2° C.

Acetanilid affords a striking illustration of the proposition that when the central vascular trunks are dilated the peripheral capillaries are contracted. Wood refers to the experiments of Hare, subsequently confirmed by Evans, in which a distinct fall of temperature was observed to have followed the use of acetanilid in normal animals allowed to run free. In a criticism of these observations he writes: "In examining the records of the calorimetric experiments made by Hare and Evans on the normal animal, we find that not only did the *rectal temperature not fall* under the influence of antifebrin, but in nearly every instance there was a *distinct rise,* amounting in some cases to over a degree. It is evident, therefore, that these experiments cannot be used to explain how antifebrin reduces temperature when it does cause a fall." In truth, they *can* be used for this purpose, but only with *dilation* of the large vascular trunks of the abdomen, and secondary *contraction* of the peripheral capillaries as factors of the process. The internal congestion caused the rise of temperature observed by Wood; the peripheral depletion caused the lowered temperature observed by Hare and Evans. And so it appears to be with all drugs we term "antipyretics" whose main effects are exercised by withdrawing blood from the surface through insufficiency of the adrenals induced by them, and transferring it to the abdominal vascular trunks. In other words, they merely remove the excess of temperature from the surface and transfer it to the internal organs.

The temperature in severe aconite poisoning is stated to undergo "a very pronounced fall," though at the very start it

[106] Phisalix: Archives de Physiologie, 1894.
[107] Bottard: Thèse de Paris, 1889.

may rise slightly: an effort of the adrenals to abnormal activity before insufficiency prevails. Alcohol, a cardiac stimulant, was found by Ruge[108] to lower the temperature 3° C. when given in sufficient quantity to animals to produce narcosis, while a lethal dose reduced it 5° C. The flushed face of the drunkard betokens adrenal overactivity with contraction of the abdominal vascular trunks and congested capillaries, while the pallor of the advanced stage typifies the contrary condition. Antimony is also stated to perceptibly reduce animal heat. Wood refers to the observation of Ackermann, who observed a fall of 6.6° C. in rabbits that lived five hours. In fact, the term "cardiac depressant" points to insufficiency of the adrenals. Insufficiently supplied with its normal tone-giving element, the suprarenal secretion, the heart is arrested in diastole. Antipyrin likewise gives rise to a fall of bodily temperature, but we have here a set of symptoms which emphasize the presence of further advanced suprarenal insufficiency: an eruption followed by a brown pigmentation. Bullæ, which recall those previously referred to as observed in children whose adrenals were found hæmorrhagic *post-mortem*, also follow the use of this drug in some cases.

Arsenic poisoning has already been referred to as simulating cholera, for which, according to Wood, it has not only been mistaken "during life, but also on the post-mortem table." It is the intense suprarenal insufficiency, similar in degree, brought on by arsenic as well as by the cholera toxin, that gives rise to the phenomena witnessed, among which is "icy coldness." Belladonna, with its alkaloid atropine, affords a good example of the antagonistic effects that always prevail. Stimulated to great activity by this drug, the central vascular trunks are contracted and the surface capillaries engorged at first. But, while a marked increase may be caused by large doses, as is well known, poisonous doses will bring it down below normal. In animals this reduction has reached 5.1° C. The bromides in toxic doses, to use Wood's words, "lower very decidedly the temperature." We have typified in the effects of these agents continued insufficiency of adrenals, just

[108] Ruge: Virchow's Archiv, xlix, 265.

sufficient to keep up moderate peripheral capillary contraction, with resulting impaired nutrition: the so-called "bromism." Dougall's case,[109] in which $1\,^1/_2$ ounces of potassium bromide was taken in 24 hours, affords a picture of total suprarenal insufficiency, weak pulse, cold extremities, temperature of 96.8° F., general cutaneous anæsthesia, coma, etc. Camphor, classed as an antispasmodic, is referred to as giving rise to "cool, pale, and livid skin" in poisonous doses. Carbolic acid, classed as antipyretic, was found by Hare[110] to produce a very distinct fall of temperature in rabbits. Chloral, a somnifacient, is referred to by Wood as follows: "A most remarkable action of chloral is upon the temperature." In this particular all observers agree with Richardson, of London, who has seen the temperature fall 6° F. in a rabbit which recovered. Hammersten observed a fall of 6° C. (Wood) in an hour in animals well wrapped up and laid in a warm place.

Chloroform furnishes a typical picture of suprarenal activity followed by insufficiency. The central trunks, at first contracted, produce engorgement of the peripheral capillaries, causing facial congestion and suffusion, accompanied by cerebral excitement. When the dangerous stage comes on, the contrary occurs: dilation of the central trunks depletes the peripheral capillaries. The heart-muscle, more or less rapidly deprived of the suprarenal secretion, gradually or suddenly fails, according to the quantity of secretion furnished its walls. These phenomena coincide with the temperature changes. Simonin[111] "found that the temperature rises during the first stage (1.1° to 0.9° C.), falls slightly during the second or remains above normal, and falls decidedly during the third stage." Cocaine, a "delirifacient," is stated to cause a "rise of *rectal* temperature in cocaine poisoning, which sometimes amounts to as much as 8° F." . . . "It is certainly not due to convulsions," says Wood, "as it usually occurs before the motor disturbance." Copper sulphate was found by Falck[112] to cause great depression of temperature. Digitalis also lowers the tem-

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[109] Dougall: Glasgow Medical Journal, Feb., 1893.
[110] Hare: Therapeutic Gazette, No. 519, 1887.
[111] Simonin: Centralblatt für Chirurgie, 234, 1877.
[112] Falck: Deutsche Klinik, vol. xi, 1859.

perature several degrees in healthy men and animals, this hypothermia being preceded by a temporary rise.

Ether was found by Angelesco[113] to lower the temperature to a greater extent than chloroform. Ether-pneumonia would thus appear to be but a manifestation of the suprarenal insufficiency started by the anæsthetic when the recuperative powers of the organs are impaired. Hydrocyanic acid acts with such promptness that the distinction between hypothermia and the increasing coldness of the extremities preceding death cannot be differentiated. Mercury was found by Kuperwasser[114] to lower the temperature 2° C., in some instances, when administered in injudicious doses. Opium and its alkaloids are referred to as causing the skin to become cold and moist when given in toxic doses. Oxalic acid in poisonous doses also gives rise to livid surface and cold skin. Phosphorus is often attended, when ingested in toxic doses, with what Wood terms "a remarkable fall in the temperature," the lowest point recorded some hours before death being 31.2° C. (88.2° F.). Physostigma brought the temperature of a strong man down to 96.6° F. Santonin poisoning is also attended with great coldness of the surface. Silver salts have likewise been found to lower the temperature of animals.

Strychnine is another agent which enables us to verify the correctness of the contention that a low peripheral temperature means an increased central temperature. Wood refers to the observations of Kionka, who showed that "the primary elevation of temperature which occurs in strychnine poisoning, both in man and the lower animals, is in animals followed by a pronounced fall, which takes place even if the convulsions persist," and to the affirmations of Mosso,[115] that "even in curarized dogs a very pronounced rise of *rectal* temperature may be produced by strychnine." Very suggestive in this connection is the denial credited to Delezenne,[116] "who states that in curarized animals the exhibition of strychnine is always followed by an abatement of the central temperature, which is

[113] Angelesco: La Semaine Médicale, Dec. 14, 1894.

[114] Kuperwasser: Archives des Sciences Biologiques de St. Petersburg, No. 6, 1898.

[115] Mosso: Archives italiennes de Biologie, 1886.

[116] Delezenne: Bulletin Médical du Nord, xxxiv, 1895.

often, but not always, followed by an increase of the temperature of the surface." This increase Delezenne explains by "the supposition that the drug has the power of dilating the peripheral vessels." It now becomes evident that the only discrepancy between the observations of Mosso and Delezenne is that the latter used smaller doses of strychnine than the former, thus producing central contraction and peripheral dilation, instead of central dilation and peripheral contraction. Tobacco, veratrum, and zinc show corresponding effects, and close the list of agents whose temperature variations are considered along with other toxic effects. All present a reduction of peripheral temperature as a sign of advanced poisoning; none show simultaneous central and peripheral hypothermia; several incidentally prove that, when peripheral hypothermia is present, there is simultaneous internal hyperthermia, thus further sustaining the view that the effects on temperature ascribed directly to drugs are of suprarenal origin.

The symptoms just reviewed and with which those associated with functional disturbances of the suprarenal glands so accurately coincide, represent the most prominent ones witnessed. There are several others, however, that are directly traceable to these organs. Of these, dyspnœa seems to point to so important a modification in the prevailing views respecting the physiology of respiration that it will be treated in conjunction with the latter function.

Cerebral Activity.—The reduction of cerebral activity—indicated by drowsiness, apathy, vertigo, coma, etc.—seems also to be—at least partly—of suprarenal origin. All drugs capable of acting as toxics apparently produce effects in this particular, corresponding exactly with those that follow removal of both adrenals or advanced Addison's disease, after giving rise to a period of excitement which also reproduces that caused by injections of suprarenal extract. We thus have again exemplified a period of suprarenal activity, followed by one of insufficiency. Four drugs taken at random—atropine, alcohol, opium, and cannabis Indica—will serve to illustrate these facts.

In atropine poisoning, the patient who, in the primary stage was talkative, perhaps violent, and showed marked evi-

dence of increased vascular pressure, including cerebral hyperæmia,—a pathological condition often observed at autopsies,—more or less suddenly lapses into a period of quietude which recalls the critical stage of many diseases. Drowsiness, confusion of thought, and coma then appear in quick succession. That we are dealing with suprarenal insufficiency is shown by the concomitant loss of muscular power beginning in the lower extremities and which may reach the stage of paralysis. Is this condition due to cerebral exsanguination? Paralysis of one of the extremities of a frog poisoned with atropine may be interfered with, according to Wood, by tying the member. This demonstrates that peripheral vascular depletion underlies the production of paralysis as well as the reduction of cerebral activity, since tying the frog's leg can have but one result: *i.e.*, prevent the return to the dilated abdominal trunks of at least a part of the blood in the limb.

Acute alcoholism probably typifies better than any condition brought on by poisons the fall from a primary intense erethism of the cerebral circulation to the opposite state through suprarenal insufficiency. The cheerfulness and the gestures of the inebriate often reach a stage of inco-ordinate excitement, mental and physical. Epileptic seizures are brought on not only in epileptics, but also, at times, in individuals that are not subject to the disease. If deterioration of the cerebral cellular elements have occurred through previous excesses and delirium tremens appear, the delirium is attended with terrors and frightful vision; if *mania a potu* prevail, the patient—perhaps gentle and kindly disposed normally—becomes furious, wild, shouts and strikes, often with homicidal intent, him or her whom he probably most cherishes.

Here, again, the suprarenal glands are shown to be primary factors of the process by the excessive muscular activity. But is the action of the secretion exerted directly upon the muscular tissues or upon the nervous structures themselves, including the centers? The action of alcohol "would seem to be due," according to Wood, "to a direct action upon the heart itself or upon the walls of the arterioles." By inserting "suprarenal secretion" instead of the word "alcohol" the process becomes clear, since it is the former which would cause

contraction of the walls of all muscular vessels and of the heart-muscle, followed by centrifugal pressure in the cerebral capillaries almost to bursting-point: the source of the intense hyperæmia found post-mortem.

In *mania a potu*, in which the most violent mania prevails, the pulse is strong, bounding, and tumultuous: an indication of correspondingly excessive suprarenal activity. When the critical stage is reached,—the first sign that the organism's protective organs, the adrenals, are losing their hold,—reason, will, and consciousness fail, and insensibility soon follows. That these organs are concerned in the production of these effects is demonstrated by the marked fall of the blood-pressure, and the rapid, thin, and compressible pulse. The lower limbs, early in this stage, have first shown their inability to support the body. "In the majority of carefully examined cases the lower limbs are affected before the upper" wrote Norman Kerr several years ago, though not aware that in this statement he pointed to a primary sign of suprarenal insufficiency.

Opium, we know, first stimulates mental activity and procures sensations of well-being. Simultaneously, muscular activity is increased—slightly in man, markedly in animals. In the latter, particularly, tremors and cramp-like contractions —true tetany—are sometimes witnessed. The vascular pressure is raised, the face is congested, suffused, and sometimes cyanosed, the skin being dry and warm. The heart's power is increased and the pulse is correspondingly full and strong. "No phenomenon of human poisoning by opium can be attributed to its action on nerve-trunks," says Wood.[117] The effects must also, therefore, be exerted upon muscular elements alone. When the crisis is reached, drowsiness lapses into deep sleep, from which the patient is roused with difficulty. If he is awakened, weakness and general prostration are more or less noticeable. The vascular pressure is lowered; pallor and cyanosis attest to imperfect oxidation; and respiration has become distant, feeble, and shallow. The heart's action is depressed and weak, the temperature low, and the skin cold and moist—all signs of suprarenal failure.

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[117] Wood: *Loc. cit.*, p. 125.

Cannabis Indica is an interesting drug in this connection, in that it seems to stimulate the adrenals just sufficiently to awaken purely psychical phenomena. This does not prevent, however, the most commonplace evidences of organic disturbance. Exhilaration, revery, ecstasy, hilarity, visions, exaltation, etc., account for the attraction possessed by some Hindoos for their *hashish*. But an overdose soon asserts the physical nature of all these phenomena. Tonic contractions, local spasms, a flushed and warm surface, heightened reflex activity, a full and strong pulse appear here as well as after poisonous doses of other drugs. When the crisis occurs, unconsciousness, paresis—beginning also in the lower extremities—a feeble and rapid pulse, attest to the effects of cannabis Indica or hashish upon the adrenals.

The list of agents in which such phenomena occur includes all those capable of causing intoxication. They all with more or less emphasis confirm the existence of a direct relationship between morbid cerebral phenomena and the suprarenal glands.

Polyuria and Anuria.—Anuria is commonly observed in animals deprived of both capsules. On the other hand, injections of suprarenal extract, as shown by Swale Vincent,[118] cause marked thirst and abundant micturition. This author also observed that the subcutaneous tissues simultaneously became distinctly œdematous. The causes of these manifestations seem clear. The reduced or arrested flow of urine resulted, in the decapsulated animals, from the immediate concentration, in the visceral vascular trunks, of blood drawn from the peripheral capillaries; the increased flow was caused by the intense increase of vascular pressure, which brought on capillary engorgement, not only of the urinary apparatus, but also of the skin. That inordinate capillary pressure underlies such a process is evident, since we not only have the hæmaturia to sustain the assertion, but also the fact, noted by Swale Vincent, that the "subcutaneous tissues were œdematous and blood-stained."

If we now turn to drugs, an interesting point suggests itself, namely: that the same effects of suprarenal overactivity

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[118] Swale Vincent: Journal of Physiologie, Feb. 17, 1898.

and insufficiency are observed *whenever the agent administered is not one which tends to inhibit metabolism of the renal cellular elements or to cause renal irritation in moderate doses.*

Opium, for instance, markedly inhibits metabolism; during the primary stage of suprarenal activity the quantity of urine is not only reduced, but complete cessation of the flow is often witnessed. We simultaneously have diminished elimination of urea and other waste-products. Copper is poisonous to all forms of protoplasm; it either gives rise to suppression or, if the dose be less active and anuria does not occur, it causes hæmaturia, and the tissues, as in Swale Vincent's animals, are blood-stained. Quinine occasions similar phenomena; hæmaturia is brought on in some cases; methæmoglobinuria—a sign of suprarenal insufficiency, as will be shown—in others. Judging by the ratio of waste-elimination, however, urea, uric acid, phosphoric acid, etc., quinine must also inhibit tissue-metabolism, and as the signs of suprarenal insufficiency only appear after very large doses, the anuria must be an attendant symptom of suprarenal activity. The anuria due to irritation may be illustrated by the effects of iodoform: a drug which readily induces inflammation of the glomeruli. Iodine also irritates the kidneys and causes nephritis when given in large doses; but these need not be such as to cause suprarenal insufficiency. Anuria, therefore, may appear along with violent cerebral excitement, a markedly increased vascular pressure and cardiac power—all evident signs of suprarenal overactivity. In two of our own cases iodide of potassium administered for syphilis gave rise to œdema of the glottis: a localized œdema of suprarenal origin. The œdema brought on by arsenic is of the same kind. In large doses it reduces the excretion of urea, and increases that of phosphoric acid and also—an important point in this connection—that of sodium chloride.

Alkalinity of the plasma, due mainly to the alkaline phosphates and carbonates it contains, is an all-important factor of the blood's physiological functions; and the sodium chloride also present serves not only to facilitate osmosis, but also to preserve the solubility of the globulins. While the water and possibly the other constituents of the urine are separated from the blood by the glomerular epithelial cells, and not by filtra-

tion resulting from blood-pressure, the fact remains that, when the quantity of blood passed through the glomeruli is augmented, the formation of urine can be correspondingly increased. The enhanced blood-pressure incident upon suprarenal overactivity may, therefore, become directly responsible for the diuresis observed when agents other than those capable of causing irritation of renal structures or of inhibiting the metabolic process of their cellular elements are employed.

These facts, collectively considered, account for the presence of many diuretics among alkaline salts, but they cannot be included among the agents capable of causing diuresis through suprarenal overactivity, because they belong to a class of remedies which *do not stimulate the adrenals before inducing insufficiency of these organs*, and the first signs of poisoning, therefore, are those attended by general depression. "No dose of a potash ever calls forth symptoms of circulatory stimulation from the human body," says Wood, referring to the diuretic salts; and, indeed, if they do, the signs are hardly perceptible. An overdose of the potassium nitrate for instance, is soon followed by a symptom complex including "collapse, great muscular weakness" . . . "with or without paralysis of the lower limbs," and "suppression of the urine in some cases"—doubtless those in which the dose was sufficiently large. A dangerous salt in this connection is potassium chlorate, which suddenly brings on most violent symptoms of poisoning: the exact symptom-complex following removal of both adrenals.

It thus becomes apparent that there are two classes of diuretics: *i.e.*, those that increase micturition through stimulation of the suprarenal glands and those that act independently of these organs—probably, in the case of alkaline diuretics, through the increased alkalinity they bring about, and liquefaction of the blood-serum they enhance. That the latter factor also comes into play when the adrenals take part in the process is probable. The supposed oxidizing power of potassium salts is probably due also, though indirectly, to the increased alkalinity which their introduction into the blood causes.

Among the true alkaline diuretics, the strontium salts alone seem to cause preliminary suprarenal overactivity. The

vegetable diuretics, buchu and uva ursi, undoubtedly do so, and it seems probable that it is only with toxic doses of their active principles—hydrochinone in the case of uva ursi, for instance—that the stage of suprarenal insufficiency can at all be reached. Digitalis gives rise to very marked symptoms of suprarenal overactivity, followed, when excessive doses are administered, by the typical signs of insufficiency.[119] Huchard aptly ascribes Petresco's remarkable results in pneumonia, in this connection, to the fact that the digitalis-leaves employed by him were rich in alkaline salts. The diuretic effect and the continued alkalinity of the plasma thus insured must certainly have done much to enable him to obtain the remarkably low death-rate reported: *i.e.*, 2.06 per cent. of 825 cases treated. The bearing of a reduced sodium-chloride ratio upon the prognosis of this disease is well known.

Among general remedies, the coal-tar products—antipyrin, acetanilid, sulphonal, etc.—may be classed with those which give rise to a short stage of excitement, attended sometimes, in the case of acetanilid, with copious urination. Here, again, all the signs observed after removal of both adrenals occur, and when anuria is absent methæmoglobinuria or hæmatoporphyrinuria sometimes appears. Yet the bladder must always be taken into account in such conditions. Wood says, for example, that this organ is completely paralyzed in advanced atropine poisoning. While forcible expulsion of urine occurs in the primary stage,—that of suprarenal activity,—the flow steadily decreases and finally ceases. "It rises and falls with the arterial pressure," observed Meuriot[120]: a strong hint that the adrenal functions are involved.

All these facts seem to us to show that *what are now considered as the cardinal symptoms of poisoning are, in reality, manifestations of overactivity or of insufficiency of the adrenals*, and *that the functions of these organs may be stimulated, inhibited, or arrested in two ways:—*

1. By a direct action of the toxic agent upon their cellular

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[119] This gives us a clue to the meaning of the supposed "cumulative" property of digitalis. Continued stimulation finally overtaxes the adrenals.

[120] Meuriot: Quoted by Wood, *loc. cit.*, p. 174.

elements and most liable to occur in acute infectious and chronic diseases and intoxications.

2. By an indirect action upon the vascular supply of the organs through a primary action upon the centers of the nervous elements that control the adrenal secretion and most liable to occur in acute intoxications by toxins, venoms, vegetable and mineral poisons.

That a simultaneous action upon both the suprarenal elements and the centers of their nervous supply may occur, however, is probable.

3. The period between the two general stages, stimulation and depression, seems to coincide with that considered in the course of acute disease as the crisis.

As toxic effects are alone involved in the foregoing processes, it is probable that:—

4. The adrenals are potent factors in the efforts of the organism to prevent the destructive effects which this selective affinity engenders, when poisons, in sufficient doses to do harm, are introduced into the circulation. This subject will again be considered in the chapter on "Immunity."

CHEMICO-PHYSIOLOGICAL PROPERTIES OF THE ADRENAL SECRETION.

Digitalis, notwithstanding its apparent predilection for the heart, affects this organ through its action upon the adrenals. But the heart-muscle is not alone stimulated by this drug; the entire muscular system responds to its action precisely as it does to that of other sufficiently active agents. Muscular overactivity, tremors, increased response to electrical stimulation, and other signs of erethism prevail. The vascular pressure is raised to such an extent in the web of frogs and in the mesentery of rabbits that the lumina of the arterioles are almost completely obliterated. The heart's action is slowed and the diastole prolonged, and when in the laboratory the behavior of the ventricles can be watched, they actually become white through the intensity of their contraction. That this is attributable to the powerful contracting effect of suprarenal extract upon muscular tissue and its constricting influence upon vessels supplied with muscular fibers, as demonstrated by

Oliver and Schäfer, seems evident. And yet, notwithstanding these effects,—those for instance which are so marked in the arterioles of the frog's web,—if we remove blood from an injected animal's peripheral vessels, even the larger ones, or blood from those of any animal, or even of a human being, a puzzling fact asserts itself, namely: this blood shows no sign of the presence of suprarenal secretion. How then does it give rise in these remote regions to the phenomena which are unquestionably of suprarenal origin?

From what has already been stated of the nervous relations of the structures directly influenced by suprarenal extract and its effects upon isolated tissues, the intervention of the nerves as a factor of the process does not even bear a superficial analysis. Another source of inquiry is available, however: *i.e.*, the possibility that the suprarenal secretion has undergone a chemical reaction in the blood, through which it has conveyed to the latter its physiological properties, while losing its own identity. This question can only be elucidated by inquiring into the chemical nature of the suprarenal active principle and the manner in which its biochemical functions are performed.

One of the first investigators to clearly define the nature of the suprarenal secretion was Gottschau,[121] who observed, in some of his preparations, projections of the medullary cells into the lumen of the central vein; he was also able to obtain, by slight pressure of the glands, blood which contained protoplasmic masses. Manasse[122] also found in man masses of medullary cells and even buds of the substance of the suprarenal capsules in the interior of veins, more frequently in the medullary than in the cortical substance. The same peculiarities were noted in the horse, the ox, the pig, and the sheep. Medullary tubes, the central portion of which was filled with brown, hyaline masses secreted by a double row of cells seen in their interior, projected into the lumen of the veins, those situated at this point being deprived of their endothelial covering. The brown, hyaline masses were thus secreted by the adrenals and carried into the circulatory stream. A. G. Auld[123]

[121] Gottschau: Archiv für Anatomie und Physiologie, 1883.
[122] Manasse: Revue des Sciences Méd. en France et à l'étranger, July 15, 1894.
[123] A. G. Auld: British Medical Journal, Oct. 4, 1894.

characterized this secretion as "colloid." Biedl[124] subsequently found these masses to consist of clear, yellow, bright granules, resembling blood-plaques or fragments of red blood-cells, though the ratio of white and red corpuscles in the vessels was normal.

The earliest chemical investigations in this connection were probably those of Vulpian,[125] of Paris, who found that the juice expressed from the suprarenal glands of various animals contained a powerful reducing substance which gave color-reactions obtainable with no other tissue of the organism. Thus, with ferric chloride, this suprarenal juice gave an emerald-green color, and with iodine solutions, a rose-carmine tint. Attempts to isolate the chromogenic substances were made by several investigators, including Virchow, Arnold, and Holm, but without success. Krukenberg[126] many years later concluded that the suprarenal chromogen was a non-volatile, nitrogenous, and ferruginous organic acid, the green color-giving substance being "more likely pyrocatechin accompanying the chromogen." An alcoholic extract prepared by Brunner[127] gave nearly all the pyrocatechin reactions, while the addition of an alkali caused it to assume a brown color. Mühlmann[128] ascribed the blood-pressure-raising power to a pyrocatechin derivative taken up with ether from the residue of fresh adrenals boiled with dilute hydrochloric acid, and which became brown on exposure to light or contact with alkaline solutions. The principal substance entering into its formation, mainly derived from vegetable foodstuffs, were, he thought, present in the blood and supposedly built up in the cortex. Recent investigations, however, have not sustained Mühlmann's views. Gürber[129] not only found it impossible to establish the relationship thought by Mühlmann to exist between the active principle and pyrocatechin, but the latter substance did not,

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[124] Biedl: Pflüger's Archiv, vol. lxvii, H. 9 and 10, 1897.

[125] Vulpian: Comptes-Rendus, vol. xliii, pp. 663-665. Quoted by J. J. Abel and A. C. Crawford, Johns Hopkins Hosp. Bull., July, 1897.

[126] Krukenberg: Virchow's Archiv, ci, 542-591, 1885. Quoted by Abel and Crawford, *loc. cit.*

[127] Brunner: Schweizer Wochenschrift für Pharmacie, xxx, 121-123.

[128] Mühlmann: Deutsche med. Wochenschrift, June 25, 1896.

[129] Gürber: Sitzungs. d. physik. med. Gesellschaft Wurzburg, 1897.

when injected, cause a rise of blood-pressure. Abel and Crawford[130] noted that it could not be isolated from the active compound by boiling with acids: a conclusion further corroborated by von Fürth.[131]

Moore[132] studied the chemical reactions noted by Vulpian from another standpoint. Having noticed that the blood-pressure-raising properties of a previously active substance disappeared after the color-reactions *were destroyed by oxidizing the reducing agent,* he was led to conclude that the color-giving constituent of the suprarenal substance was the same as the blood-pressure-raising constituent. The solubilities of both were similar, while both, also, were found only in the medulla or in the suprarenal vein. Manasse[133] obtained from the suprarenal medulla a substance resembling greatly in chemical properties Drechsel's jecorin, but its reducing power was found to differ in several particulars from that described by Vulpian and Moore. Fränkel,[134] by utilizing the more advanced methods of organic chemistry, also reached the conclusion that Vulpian's chromogen and the blood-pressure-raising constituent were identical, and called it "sphygmogenin": a nitrogenous derivative of the orthodioxybenzine series. He succeeded in isolating the jecorin-like body obtained by Manasse and Vulpian's reducing substance, and attributed to the latter the blood-pressure-raising attributes.

A closer investigation of the whole subject was then undertaken by J. J. Abel and A. C. Crawford,[135] of Johns Hopkins University, who recalled that all previous work had brought forth conclusions based on reactions made with aqueous, alcoholic, or acetonic extracts only, and that so far no definite chemical compound had been isolated. They found, by isolating the blood-pressure-raising constituent, Vulpian's chromogen, in the form of a benzoate, and, decomposing it, that the active principle was a substance which could, in all probability, be classed with the pyridine bases or alkaloids, or the pyrrol

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[130] Abel and Crawford: Johns Hopkins Hosp. Bull., July, 1897.
[131] Hoppe-Seyler: Zeitschrift für Physiol. Chemie, vol. xxiv.
[132] Moore: Journal of Physiology, vol. xviii, p. 230.
[133] Manasse: Zeitschrift für Physiol. Chemie, vol. xx, p. 478, 1895.
[134] Fränkel: Wiener med. Blätter, Nos. 14, 15, and 16, 1896.
[135] J. J. Abel and A. C. Crawford: Johns Hopkins Hosp. Bull., July, 1897.

compounds. In a subsequent paper Abel[136] announced that he had isolated the active principle of the suprarenal capsule in the form of a light-gray or brownish powder whose percentage composition could be expressed by the formula $C_{17}H_{15}NO_4$. This approaches in elementary composition several alkaloids, namely: pseudomorphine, represented by $C_{17}H_{19}NO_4$; cocaine, the formula of which is $C_{17}H_{21}NO_4$; while sanguinarine, whose power to raise blood-pressure is noteworthy, is represented by $C_{20}H_{15}NO_4$. Again, in the course of previous work, Abel and Crawford had noticed that suprarenal extract, entirely free of proteids and physiologically active, gave a pyrrol reaction on dry distillation, as evidenced by the odor and various tests. Alkaloids—morphine, for instance—also give pyrrol on dry distillation; while, on the other hand, pyrrol compounds, to which Abel's active principle—called by him "epinephrin"—belongs, are known to possess marked blood-pressure-raising properties. While the free base prepared at high pressure, or its salts, is not active in this particular, the free base prepared at low pressure is very active, and, of its salts,—the benzoate, picrate, hydrochlorate, hydrobromate, and sulphate,—the latter is most particularly so. Its identity is also demonstrated by the fact that, as is the case with suprarenal extract, its effects are ephemeral; small doses intravenously injected at first excite, then centrally depress, respiration, heart-failure following the use of large doses. Again, its kinship to chromogens becomes apparent through the fact that uroerythrin, the normal pigment principle of the urine, exhibits properties very similar to epinephrin. Finally, active suprarenal extractives are known to be *very prone to become oxidized;* this tendency is so marked in the case of epinephrin that it is a source of great inconvenience. Von Fürth, of Strassburg,[137] has also produced an active principle which he has termed "suprarenin," but this product does not seem to show properties superior to those of epinephrin. J. Takamine[138] has more recently contributed a preparation which he has named "adrenalin," the physiological activity of which is said to be remarkably powerful, a fraction

[136] Abel: Johns Hopkins Hosp. Bull., Sept.-Oct., 1898.
[137] Von Fürth: Journal für prakt. Chemie, Bd. xxix, S. 105.
[138] J. Takamine: Therapeutic Gazette, April 15, 1901.

of a drop of a solution of 1 to 10,000 being sufficient to blanch the conjunctiva. It was found to be equally active as a blood-pressure-raising substance, $^1/_{200000}$ gramme intravenously injected into an adult man being sufficient to produce a distinct effect.

A striking feature that a review of the biochemical work done in this direction discloses is the peculiar property shown by the various preparations of suprarenal gland and its extractives to become oxidized. Abel has found this feature so marked, for example, that it caused him, as we have seen, considerable inconvenience. Takamine states that the colorless, aqueous solution of adrenalin is easily oxidized by contact with the air, its color changing from pink to red and eventually to brown. Cybulski also observed that the addition of weak doses of permanganate of potassium destroyed the activity of the suprarenal extract, and held that the office of the active principle was to sustain the activity of the vasomotor and respiratory centers, the vagi and accelerator nerves, and probably also the center which maintains the muscular tonus. He also thought that oxidation might account for the temporary effects which injected suprarenal extract produced. His views were shown to be erroneous by Oliver and Schäfer, however, and indirectly by other physiologists. Yet, while Cybulski's hypothesis is untenable, the remarkable affinity for oxygen shown by suprarenal extractives remains and affords a solid chemical foundation upon which our inquiry can be based.

By what process could this property to become oxidized enable adrenal extractives to induce the contraction of muscular tissues which underlies blood-pressure-raising power? Besides their pressure-raising power, these extractives also possess a property which may elucidate some phases of the problem before us, namely: the fact that injections of suprarenal extract counteract, at least for a time, the morbid phenomena witnessed after removal of both adrenals. This, in a measure, refers us to the liver, and it may prove profitable to first study the relations of this organ with the toxic phenomena which removal of both adrenals awakens. Especially is this probable since we have control evidence in the fact that a large number of investigators have observed that the toxic symptoms thus

caused could be counteracted by injections of suprarenal secretion. Thus, Abelous and Langlois[139] found that the fatal effects of removal of both organs in frogs could be delayed by the insertion of small pieces of the removed gland into the dorsal lymph-sac, and also by injections of suprarenal extract. Cybulski[140] also noted that intravenous injections of 1 cubic centimeter of a 10-per-cent. solution of suprarenal extract caused all the toxic phenomena to disappear after the extirpation of both adrenals, the effect lasting from a few minutes to one-half hour. In normal animals the extract merely increased pressure, lowered the pulse-rate, and accelerated respiration.

The oxygen-ratio of hepatic tissue first claims our attention, since it is possible that the suprarenal secretion might lose its identity as such by yielding to the liver some of its own molecular constituents: *i.e.*, constituents endowed with less affinity for the remaining suprarenal components than for structures containing, as does the liver, a high ratio of fixed oxygen. The labors of Schmiedeberg, Jaquet, and Salkowski[141] may advantageously be used to ascertain this point.

Schmiedeberg, to study the oxidation of living tissues, used benzilic alcohol and salicylic aldehyde, because these substances do not burn in air, while they are easily consumed in the organism. Their oxidation products could only, therefore, originate in the latter. Jaquet[142] also demonstrated the correctness of Schmiedeberg's observation that the blood alone caused but an extremely small quantity of benzilic alcohol to become oxidized into benzoic acid, while salicylic aldehyde was in no way influenced. His researches further confirmed Schmiedeberg's discovery that, when these agents were simply dissolved in the blood, they were easily oxidized into benzoic acid by living tissues. The blood, as a whole, seemed to retard oxidation, since the process occurred with greater rapidity when blood-plasma alone—*i.e.*, serum devoid of all its corpuscular elements—was used as a solvent. Not only was lung-tissue, for instance, found to act perfectly as an oxidizant, but

[139] Abelous and Langlois: Archives de Physiologie, vol. xiii, p. 267, 1892.

[140] Cybulski: Gazette Lekarska, March 23, 1895.

[141] Schmiedeberg, Jaquet, and Salkowski: Archives Générales de Médecine, March, 1898.

[142] Jaquet: Archiv für exp. Path., 1892.

frozen lung-tissue, as hard as wood, as well. Horse-lungs and kidneys kept from twelve to fourteen days in alcohol at seventy-five degrees, even after having become sodden with physiological saline solution, etc., were found fully active. Abelous and Biarnés[143] successfully used blood alone as an oxidizant, but *only when a continuous current of air* traversed the blood treated with salicylic aldehyde. Schäfer and subsequently Auld also observed that the activity of suprarenal extract was not in the least impaired when blood and the extract were mixed *in vitro* even when allowed to stand some time.

Salkowski[144] repeated the experiments of Schmiedeberg and Jaquet, in order to ascertain the differential oxidizing powers of various viscera. The following proportions of salicylic acid were obtained from salicylic aldehyde placed in contact a definite time with 100 grammes of the following organic tissues: Liver, 138 milligrammes; spleen, 110 milligrammes; kidneys, 22 milligrammes; pancreas, 2.8 milligrammes; and muscle, 1.4 milligrammes. This clearly demonstrates, at least, that the liver and spleen are by far the organs that take up and fix the greatest proportion of oxygen, and that, of all organs, the liver is the most active oxidizing agent. Now, Langlois found that maceration of hepatic tissue with suprarenal extract greatly decreased the activity of the latter. The remarkable affinity for oxygen possessed by the extract normally suggests that, like salicylic acid, it must have become oxidized at the expense of the liver-tissue and that it is through this reaction that its activity became impaired. Still, the contrary might be the case and the liver acquire its own oxygen-storing properties from the secretion of the adrenals and take it up from the blood while the latter is in transit through it. Under these circumstances it would also acquire the blood-pressure-raising power of the secretion. That such is not the case, however, is evident. Swale Vincent could not obtain the effects of suprarenal extract with either liver or spleen extracts; neither could Mankowsky[145] from extracts of liver, pancreas, thyroid, lymphatic glands, parotid, kidney, spleen, cerebrum,

[143] Abelous and Biarnés: Archives de Physiologie, 1895.
[144] Salkowski: Virchow's Archiv, Jan. 4, 1897.
[145] Mankowsky: Russian Arch., March, 1898.

heart, or even of muscle. Evidently, therefore, the great affinity of the suprarenal extractive for oxygen caused it, as had the salicylic aldehyde, to *take up and fix* the hepatic oxygen, and the fact that in doing so *it lost its activity* appears to us to indicate that its physiological functions are in some way connected with this property.

If the affinity of the suprarenal secretion for oxygen is the source of its physiological activity, where would the useful reaction occur? The first important vessel reached by the secretion is the inferior vena cava. As veins contain blood which has served its purpose in the organism, it is not likely that this blood should be utilized otherwise than as a vehicle. Again, that it is not in the blood of the vena cava that the secretion undergoes a reaction is obvious; it enters the blood-stream near the heart: *i.e.*, where the proportion of oxygen is normally at its lowest ebb. That this acts only as a carrier for the secretion, therefore, is evident. Yet there is a very interesting and suggestive feature connected with the itinerary of the secretion and which bears directly upon the question in point. Biedl and Szymonowicz undoubtedly found the secretion in the vessels near the adrenals, but *not in other veins of the organism.* Blood drawn from the suprarenal vein gave rise, when injected into the blood-stream of a normal animal, to manifestations similar to those observed after the injection of suprarenal extract, while injections of blood taken from other veins were followed by negative results. The suggestive feature referred to is that the limits of the organs in which the reaction must occur become restricted to the neighborhood, as it were, of the channels in which the secretion first appears. What are the limits of this "neighborhood?"

The inferior vena cava supplying nothing capable of suggesting a reaction in its blood, the secretion must reach the heart, and, if it does, its presence must in some way become manifest, since we have seen how powerfully this organ responds to the action of suprarenal extract. But, of course, it is necessary to ascertain whether it reaches the heart under normal conditions. Digitalis, owing to its well-known action upon the heart-muscle, suggests itself as a ready means for this purpose. Indeed, its toxicology not only associates it di-

rectly with suprarenal functions, but it constitutes one of the most active suprarenal stimulants, judging from the character of the symptoms to which it gives rise. Striking, for instance, is the fact that its action is greatest on the *right side of the heart*: a fact emphasized by many authorities, including Ringer, François Franck, Hale White, Germain Sée, and Openkowski. As *this is the side which the suprarenal secretion would first reach*, a strong indication is afforded that the stimulation we ascribe to digitalis itself is really induced by the secretion of the adrenals. It is evident, however, that the myocardium cannot supply the required oxygen, since it only stands 1.4 milligrammes as a muscular structure to the liver's 138 in Salkowski's series. Again, its structure and physiological functions in no way indicate a connection with any chemical change in the fluids that pass through it.

The next organs are the lungs, the tissues of which, according to Abelous and Biarnés, occupy a third place as oxidizing agents in the experimental series: *i.e.*, immediately after the spleen and liver. Yet, the reaction cannot occur in the parenchyma to which these experiments refer, since, judging by the effects of the suprarenal secretion throughout the entire body, the whole volume of blood submitted to the respiratory process must be utilized. May the suprarenal secretion be a physiological factor of the respiratory gaseous interchanges?

Among the symptoms observed after the extirpation of both adrenals is dyspnœa. When the physiological and pathological origin of this symptom is analyzed in the light of the views submitted in the foregoing pages, the possibility that the respiratory process may in some way be connected with the suprarenal glands imposes itself. This can be illustrated by what appears to us to be a sudden awakening of suprarenal activity by one of our best agents for this purpose, strychnine. "It produces in the dog," says Wood, "an extraordinary increase in the respiratory movements"; his experiments have shown that this "never amounted to less than 75 per cent., and sometimes rose to 300 per cent." He refers to Kionka's observation, confirmed by Obermeier,[146] that "in the rabbit there is a

[146] Obermeier: Inaugural Dissertation; Erlangen, 1891.

notable increase in the production of carbonic acid: *i.e.*, of oxidation." Kionka[147] is also stated to have found that "blood taken from the strychninized animal did not absorb oxygen with the avidity of normal blood, although no spectroscopic changes could be discovered in it. We are evidently in the presence of an inordinate and excessive functional manifestation: *i.e.*, an extraordinary increase in the respiratory movements, of oxidation, and of CO_2 production. That such is the case is sustained by the fact that this oxygen-laden blood does not absorb *in vitro* as much O as would normal blood. It is further branded as a result of excessive function by the absence of spectroscopic changes.

The corresponding effect of toxic doses of suprarenal extract is well shown by Swale Vincent,[148] who states: "In cats, by far the most noticeable feature was an enormous rapidity of the respiratory movements in the early stage. . . . In one frog the condition induced appeared to resemble that of strychnine or veratrine poisoning. On touching the animal a short series of spasms set in. But that the effects were not due to the spinal cord was shown by its destruction, when the condition of the animal was apparently the same as in another with cord intact." In rats he found that doses of 0.25 to 0.5 gramme of dried suprarenal gland produced "quick and shallow respiration." It seems clear that toxic doses of suprarenal extract give rise to increased respiratory activity, and furthermore that these effects did not originate in respiratory centers. Neither can the effects of strychnine be asserted to be of central origin. "On chloralized dogs the respiratory effects of the alkaloid were even more pronounced," writes Wood. The paralyzing effects of chloral upon the medulla are well known. All these facts, collectively considered, seem to strongly suggest that dyspnœa and other respiratory phenomena are due to variations, qualitative and quantitative, of the suprarenal secretion, and directly associated with the functions of the glands themselves.

This conflicts with the generally-accepted teachings concerning the effects of poisonous blood upon the respiratory

[147] Kionka: Archives de Pharm. Inter., vol. iii, 1898.
[148] Swale Vincent: Journal of Physiology, vol. xxii, No. 4, Feb. 17, 1898.

centers, and particularly with the view that these centers "may be excited both by blood that is rich in carbon dioxide and by blood that is poor in oxygen." And yet there probably does not exist in the whole domain of physiology a question admittedly more obscure, and in which ingenious theories have proven more sterile. A reduction of the oxygen in the blood is thought to impair central functions, although there is ample experimental evidence to prove that such is not the case. The blood of an animal may in great part be removed and replaced by saline solution and its breathing continue as quietly and regularly as before the procedure. The same results have been obtained even in frogs from which the heart had been removed. As elsewhere in the organism, the functions of the medullary centers occur in virtue of the molecular changes, which must normally be enhanced, if at all, by an excess of oxygen and inhibited by an excess of carbonic acid. How can, therefore, the latter give rise to increased respiratory activity?

That considerable uncertainty prevails in this connection is shown by the following lines by Professor Foster[149]: "A lack of oxygen in the blood, or a nervous impulse along an afferent fiber, both affect the center by modifying its metabolism; but each probably affects it in a different way. It is beyond our present knowledge to explain how either the one or the other acts. We may imagine that a lack of oxygen, on the other hand, has a more profound effect in modifying the whole complex series of metabolic changes, the whole chain of building-up and breaking-down processes, thus in some way or other rendering the whole edifice, so to speak, more unstable; and that an afferent augmenting impulse (and possibly an excess of carbonic acid) acts rather after the fashion of what we are accustomed to call a stimulus, and fires off a larger amount of the already stored up explosive compounds. And we may further imagine that the special feature of the substance of the respiratory center is that the metabolism is so arranged as to be thus, unlike that of other living substances, rendered unstable and more explosive, not simply diminished

[149] Foster: "Text-book of Physiology," p. 383.

or deadened by a lack of oxygen. But these, as yet, are matters of speculation."

The clinical evidence which could be adduced to emphasize a relationship between the respiratory functions and the adrenals is very great. Several of the more prominent symptoms of the algid stage of Asiatic cholera, for instance, when considered collectively,—cyanosis of the extremities and face, increased frequency of the respiratory movements and dyspnœa, etc.,—point to the lungs as the seat of morbid phenomena. Cyanosis obviously denotes insufficient oxygenation whatever be its cause, while imperfect oxygenation in turn implies an increase of the carbonic-acid ratio. That this gas accumulates in the organism during cholera has been demonstrated. The connection is further suggested by the symptoms that follow extirpation of suprarenal glands in mammals; so closely do they resemble those of Asiatic cholera as to suggest that we have in this disease the characteristic symptom-complex of arrested suprarenal function. Besides the general manifestations, which will be reviewed later on, those pertaining to general vital processes, oxygenation, temperature, etc., are similar in both conditions. Both show great reduction of vascular pressure, with consequent small and rapid pulse, while both are alike attended by "increased frequency of the respiratory movements, dyspnœa, and often cyanosis and subnormal temperature" during what might be termed the algid stage of both morbid states, which are also similar in this particular. If, then, the symptoms referred to are traceable to the lungs in cholera, we are warranted, we think, in ascribing those that occur after extirpation of the adrenals also to the lungs. Especially is this permissible since we are led to the lungs for a reaction which the chemical properties of the adrenal secretion render possible, and since they are so anatomically disposed as to make it possible to distribute the charged blood, through the agency of the heart, to all the tissues of the organism.

Indeed, the more the inquiry progresses in this direction, the more does it become evident that an important relationship exists between the suprarenal and the pulmonary functions. A striking feature is the apparent exemption of the pulmonary tissues to the effects of suprarenal secretion. Wal-

lace and Mogt,[150] of Ann Arbor, found that, while suprarenal extract caused a rise in the systemic blood-pressure due to the contraction of the arterioles, the pressure in the pulmonary arteries was not raised, these vessels, in their opinion, not being acted upon as are the others. Velich,[151] on the other hand, found, by a series of experiments instituted to ascertain whether vasoconstrictor fibers existed for the pulmonary vessels, that suprarenal extract gave rise to but a slight rise of pressure: a result which led him to conclude that the existence of a special vasoconstrictor mechanism, either central or peripheral, for the pulmonary circulation, could not be considered as established. Warm suprarenal extract, which, when applied even to the skin, causes pallor, was found by him to exercise no such effect upon the surface of the lungs. Briefly, upon all other tissues the effects of suprarenal extract are strongly marked; as soon as the pulmonary structures—where the conversion of venous blood into arterial blood occurs—are reached, its powers practically cease.

True, the physiology of respiration as at present interpreted in text-books and as generally taught would not be sustained. This does not mean, however, that all physiologists have finally accepted the prevailing doctrine based on the diffusion of gases. Indeed, there is considerable experimental evidence based on the labors of Robin, Bohr, Müller, and others to show that it is by no means invulnerable. "When," says Prof. Mathias Duval,[152] of Paris, "an animal is caused to breathe in the smallest possible space—the air imprisoned in its lung by strangling—it uses up all the oxygen of this air. This is because hæmoglobin, in virtue of its chemical affinity, takes up the oxygen as fast as this gas is dissolved in the serum, so that the latter, always despoiled, is never able to satisfy its absorption coefficient for oxygen, however low be this coefficient, and however slight be the tension of the oxygen in the surrounding air. As to the exhalation of carbonic acid, it is not produced in so simple a manner as would *a priori* seem, by mere gaseous diffusion or by the mere giving off of a gas in solution, because

[150] Wallace and Mogt: Transactions of the Physiological Society, Dec. 28-30, 1898.

[151] Velich: Wiener med. Wochenschrift, No. 26, 1898.

[152] Mathias Duval: Cours de Physiologie, Ed., 1892.

of the scarcity of the gas in the surrounding atmosphere. Indeed, the air in the pulmonary vesicles contains 8 per cent. of carbonic acid, hardly a favorable condition for the escape of carbonic acid from the blood, especially since a portion of this gas is not dissolved, but combined with the serum salts. It is therefore probable that the pulmonary tissues are the seat of an action having for its object to rapidly dislodge the carbonic acid. *This action is probably of a chemical nature.*[153] . . . Whenever oxygen is mixed with venous blood, even *in vitro* during experiments, the carbonic acid is immediately given off. One is led to admit, therefore, that the combination of oxygen with the blood-corpuscles (oxyhæmoglobulin) plays a rôle analogous to that of an acid, and involving the elimination of carbonic acid from venous blood." He refers to Robin and Verdeil's view in respect to the existence of a hypothetic "pneumonic acid" and to the experiments of Garnier,[154] who observed that ultramarine blue sprayed into the lungs of living guinea-pigs lost its color: a phenomenon which could only occur through the presence of a strong acid, neither taurin nor carbonic acid being capable of producing it. "Chemical analysis of the lung has not disclosed a specific acid, however." . . . "It is, perhaps, wrong," adds Professor Duval, "for physiologists to continue to only see in these phenomena mere results of endosmosis of liquids and of diffusion of gases through an inert membrane."

To study this question satisfactorily, however, and place the deductions reached upon a strong footing, it is necessary to clearly define the relations between the various bodies concerned in the process. All the phases of the problem, physiological and pathological, must therefore be analyzed. The following facts, however, seem to afford a firm foundation for the inquiry:—

1. The adrenals secrete a colloid substance which penetrates the lungs with the venous blood and cannot be traced beyond these organs.

2. The secretion of the adrenals possesses a marked affinity for oxygen.

[153] The italics are our own.

[154] Garnier: Comptes-Rendus de l'Académie des Sciences, July 26, 1886.

CHAPTER II.

THE INTERNAL SECRETION OF THE ADRENALS IN ITS RELATIONS TO THE RESPIRATORY PROCESSES AND THE COMPOSITION OF THE BLOOD.

THE PATHOGENESIS OF BRONZING AND ADDISON'S DISEASE.

Boinet[1] found a large proportion of black pigment and hæmatoïdin crystals in the blood of a decapsulated rat which had lived several months after removal of its capsules. This pigment proved on analysis to be similar to that obtained from the skin, mucous membrane, and other structures of two fatal cases of Addison's disease. The identical black pigment was also found by him in more or less great quantities in 75 per cent. of 109 decapsulated rats. It was distributed practically everywhere, including the lungs. In several of these animals and in a number out of another series of 20 in which the adrenals had been experimentally cauterized with tincture of iodine, silver nitrate, ferric chloride, or zinc chloride, or irritated with pus from inflammatory or tuberculous lesions, the pigment had permeated the subcutaneous cellular tissue besides the other structures. In 3 animals in which the pigment infiltration had been abundant, the adrenals had not only been removed, but excessive fatigue had been induced by rotation or frequently repeated electric shocks. All the rats from which the glands had been removed sooner or later presented the characteristic signs that follow this operation. Some of those in which the organs had been cauterized showed "marked muscular paresis with tardy asthenia: features that gave them the aspect of incompletely curarized animals and which further completed the analogy between the pigmentary infiltration and a sort of Addison's disease."

The liberation of this pigment through removal of the adrenals suggests as a working hypothesis that *the secretion of*

[1] Boinet: Marseille Médical, April 15, 1896.

these organs serves to keep united or hold together various bodies entering into the formation of hæmoglobin and that *it is concerned with the affinity of this compound for oxygen.*

In man the blood-pigment is more soluble than in animals, and the likelihood of observing similar effects in human blood to those witnessed in that of Boinct's rats is slight. Cutaneous pigmentation and the pigments observed will, therefore, have to form the basis of our inquiry. The first affection to present itself, Addison's disease, will serve a double purpose; it will not only enable us to trace a closer connection between the respiratory blood-changes and suprarenal secretion, but also the manner in which the adrenals exercise their prophylactic mission notwithstanding the inroads of local organic disease.

Bronze spots have been observed in connection with a variety of disorders in which the adrenals were apparently normal: abdominal growths, diabetes, exophthalmic goiter, tuberculosis, chronic gastric and hepatic disorders, hysteria, pulmonary sarcoma, cholangitis, etc. To conclude, however, as some authors have done, that the adrenals are not involved in Addison's disease or in any other disorder is doubtless injudicious, since any disease may directly or indirectly implicate the central or extrinsic nervous structures of the organs, inhibit their nutrition, disturb their metabolism, and in this manner give rise to organic lesions only appreciable microscopically. Indeed, it must be admitted that much of the work reported in this connection is quite valueless and, in fact, misleading. Arnaud, as already stated, found, in one hundred adrenals picked up *at random* at autopsies, thirty-six which microscopically showed more or less marked lesions. What can the statement that "the suprarenal glands were found normal" based upon a macroscopical inspection of the organs be worth under these circumstances?

A single perfectly normal adrenal, we have seen, can compensate for an inactive or extirpated mate, and, as no bronzing seems to follow unilateral adrenalectomy, we can at least surmise that this symptom will not appear unless the functions of both organs are simultaneously compromised. This is sustained by the six cases of adrenal hæmorrhage out of the eighty collected by Arnaud, in which true bronzing was present. A

review of each of these will prove interesting. In a case credited to Mattei[2] the skin of the face, neck, forearms, and hands was bronze-like, while marked muscular debility was complained of. The accompanying broncho-pulmonary congestion with emphysema and valvular disorder did not account for the bronzing. At the autopsy both adrenals were found hæmorrhagic. In Carrington's[3] case the bronzing was especially marked over the mammary glands, the penis, and scrotum, and the patient died of progressive asthenia. Both lungs were found œdematous and dark, and both adrenals diseased and probably cancerous. In Murray's[4] case the skin was described as brown; there was dyspnœa, cough, and asthenia, but the patient's illness only lasted four days. Both capsules were hæmorrhagic. Less clearly defined is a case reported by Northrup,[5] in which an "abnormal color" was associated with hæmorrhage into both capsules. In Leconte's case the discoloration is termed "swarthy," with large sepia-like spots, discovered after death. The case was one of pulmonary tuberculosis, but unusually cachectic. No tubercular foci were found in the adrenals; one of these was atrophied and the other was studded with hæmorrhagic *puncta* the size of a millet-seed. In Rayner's[6] case a "marked olive hue" is referred to, the patient suffering from bilateral bronchitis and pain in the lumbar region. Death occurred suddenly and both adrenals were found hæmorrhagic. The interesting feature of these six cases is that they are all associated with organic lesions of *both* adrenals, while all cases (excepting two in which the discoloration is obviously ascribable to other disorders) with only one organ diseased show no discoloration. This does not mean, however, that bilateral organic lesions always cause bronzing, inasmuch as there were twenty-seven of such cases in which no discoloration appeared, but it emphasizes the fact that, *when bronzing occurs, both adrenals are diseased or functionally insufficient.*

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[2] Mattei: Lo Sperimentale, p. 386, Case III, 1883.

[3] Carrington: Transactions of the Pathological Society of London, 1885.

[4] Murray: Transactions of the Pathological Society of London, vol. xxi, p. 396, 1870.

[5] Northrup: Proceedings of the New York Pathological Society, p. 161, 1889.

[6] Rayner: Cited by Roger in l'Expérience, May 10, 1837.

But why does bronzing not occur in all cases of bilateral organic lesion? To study this feature of the problem we must first eliminate all cases in which the cutaneous changes could not have had time to develop. Burns, traumatisms (including compression of the funis or of the body at birth), asphyxia, and toxic processes of various kinds can suddenly produce hæmorrhage into both organs simultaneously and cause death long before any such symptom as bronzing can at all be produced. Almost all hæmorrhages observed, in fact, appear to be of recent date. To ascertain the point in question we must, therefore, not only utilize cases in which very clear *post-mortem* data are furnished, but also cases in which both glands can be shown to have been diseased sufficiently long to have involved both the parenchyma and the cortex and to have caused bronzing through complete structural disorganization.

Of the eighty cases collected by Arnaud, but two appear in which both suprarenal capsules seem to have been sufficiently diseased to lead us to expect the appearance of bronzing if complete structural disorganization of these organs in its evolution can give rise to this symptom. In Goolden's case[7] all the symptoms of Addison's disease were present except bronzing. The autopsy revealed that both organs were practically destroyed. Yet the left organ still contained a *small quantity of medullary substance*, and the acute symptoms had come on *suddenly a few months before with as suddenly developed anæmia.* The second case is one of Arnaud's, in which both organs were transformed into large organized hæmatomata. The patient having been brought into the hospital in a comatose condition, his history could not be traced; but there was no bronzing. The histological data of the neoplasms clearly indicate that they were not of recent formation, while no other visceral lesion could be detected. But again do we find a *small area of normal parenchyma* in the right capsule. Can we attribute the continuation of the organ's functions and the absence of bronzing to the presence in both cases of these remnants of suprarenal medulla? We probably can, since the work of various investigators—Gourfein particularly, as pre-

[7] Goolden: Lancet, p. 266, vol. ii, 1857.

viously stated—tends to show that one-twentieth of both glands suffices for the continuation of those functions for a given time.

In the light of all that has been incorporated in this work so far, these cases suggest an explanation of the causes of bronzing which it might be well to outline before going any farther. Collectively considered, the data alluded to suggest that *any case of suprarenal disease may proceed to death without reaching the stage of bronzing*, for, in all instances in which this symptom occurs, the suprarenal insufficiency, whether due to intrinsic or extrinsic disease, must have reached a correspondingly advanced stage. Disease of any structure which directly or indirectly nourishes or innervates the adrenals, or any organic lesion of the organs themselves, can thus inaugurate a condition that will lead to their physiological insufficiency both quantitative and qualitative. But, and this is the important feature: *the integrity of the organs must be greatly compromised before their all-important functions become implicated in the morbid process*—so great is the supply of cellular reserve which Nature has granted them, or so small perhaps, in proportion to its potency, is the amount of secretion required to satisfy the needs of the systemic functions which they normally supply. *It is only when this minimum limit of normal activity is passed that the stage of bronzing begins*, preceded or soon followed by the earlier symptoms of Addison's disease. The latter would thus represent but an advanced stage of slowly progressive suprarenal insufficiency brought on by a pathogenic cause of any kind.

The application of this conception to the many paradoxical phases which Addison's disease presents in respect to its main symptom, bronzing, singularly clears the field, besides affording a basis for all the theories, based on careful study, which have been advanced so far concerning the origin of this symptom.

If Lewin's proportion of caseous glands in Addison's disease, 74 per cent., and Gilman's, 80 per cent., are considered collectively,—*i.e.*, 77 per cent.,—we are only obliged to account for 23 out of 100 cases which do not present tuberculous lesions of the adrenals. For this purpose we have at our disposal all the diseases to which the nervous, vascular, and lym-

phatic supplies of the organs—including, of course, their cerebro-spinal connections — are liable. The pericapsular nerve-ganglia, for example, which, according to Alezais and Arnaud,[8] may be diseased without implicating the nerves and ganglia of the solar plexus, have been so often found the seat of lesions by these clinicians that, in their opinion, bronzing only occurs when these structures are diseased. Lesions of the sympathetic have so frequently been noted by Lancereaux[9] when bronzing is present that he ascribes this symptom only to extensive disease of the nerves and ganglia of the abdominal sympathetic. That all nervous structures peripheral to the adrenals are involved in the pathogenic process of bronzing has been contended by Fenwick, Greenhow, Jurgens, Raymond and other observers. At the origin of the nervous structures, the spinal axis, Kalendero and Babès[10] found chronic sclerosis of the posterior roots, with marked swelling of the axis-cylinders of the spinal nerves, as main features of a typical case. Bonardi[11] noted in another instance spinal lesions exactly similar to disseminated myelitis of toxic origin. Thus any disease of the nervous supply including the cord may be etiologically associated with bronzing, but only when, as is the case with local lesions, the morbid process is far advanced. This is readily accounted for when we consider the wide margin of glandular substance present, which likewise insures the continuation of physiological functions even under greatly impaired innervation. Disease of the semilunar ganglia or of any other nervous structure might thus exist, as it often does, without causing physiologically perceptible lesions of the adrenals. The vascular lesions are, briefly, those of the general vascular supply, particularly atheroma.

A kinship to some cardiac valvular lesions is also suggested by the presence of valves in the veins of the capsular plexus, emptying into the lumbar vein, as shown by J. M. Flint,[12] who says: "Thus the circulation in the medulla depends somewhat on the condition of pressure in the lumbar vein, and stagnation

[8] Alezais and Arnaud: La Semaine Médicale, Oct. 7, 1891.
[9] Lancereaux: Archives Générales de Médecine, Jan., 1890.
[10] Kalendero and Babès: La Semaine Médicale, Feb. 22, 1889.
[11] Bonardi: Revue Neurologique, Aug., 1897.
[12] J. M. Flint: Johns Hopkins Hosp. Reports, vol. ix, 1900.

of the blood-current in the vena lumbaris would induce a congestion in the venous tree of the medulla." If we recall the pathogenesis of suprarenal hæmorrhage as reviewed in the earlier portion of this work, the connection between this condition and possible valvular lesions of the adrenals will appear. The lymphatic glands bear the same relations to these organs as the nervous system, and give rise to bronzing when in addition to tuberculous processes in distant chains, the peribronchial, cervical, etc., the abdominal lymphatics are sufficiently diseased to seriously interfere with the suprarenal functions. This sometimes occurs when the abdominal glands alone are affected, as was the case in an instance recorded by Henry Waldo.[13] Their important connection with the diseases which most frequently cause structural lesions of the organs—tuberculosis, cancer, etc.—obviously gives them a prominent position in their pathology.

Under all these conditions, even with advanced peripheral disease, the organs may appear normal macroscopically and their functional integrity be so compromised as to give rise to bronzing. Structural destruction of one adrenal and functional inhibition of the other through peripheral lesions may also occur simultaneously and thus lead to the belief, at the autopsy, that one organ was normal. Again, the great margin of functional power with which these organs are endowed places beyond question the fact that long before a sufficiently extensive involvement of both organs can have occurred the patient may die, all the stages of organic lesion appearing post-mortem. Vulnerable in the extreme, these cases, if the general affection does not carry them away before bronzing will have had time to appear, sink rapidly under the effects of any intercurrent disease, a slight toxæmia, or any condition which spurs their infirm adrenals into any degree of activity beyond the normal needs of the organism.

All this does not necessarily mean that because pigmentation is present the case is nearing its end in every instance. The causative disorder may become, so to say, latent, and the diminished glandular activity suffice for the more or less per-

[13] Henry Waldo: British Medical Journal, July 10, 1897.

fect performance of physiological functions, if the insufficiency be not too far advanced. The bronzing of tuberculosis, syphilis, and chronic arsenic poisoning offers many examples of this kind. Syphilitic cases under specific treatment may sometimes be brought to a condition suggesting recovery, for instance. Oestreich[14] witnessed such a result in a case of Addison's disease in which a tuberculous adrenal was removed under the belief that it was a malignant growth. All the typical symptoms of the disease disappeared after the operation, and complete recovery ensued. This clearly indicates that the toxic process caused by disease of the one gland induced insufficiency of the other, and that as soon as the morbid source was removed what was left normal of the other organ was sufficient for the continuation of life.

As already stated, hypertrophy of the glandular tissues to meet an increase of physiological work has been brought on experimentally by several investigators, Stilling,[15] Charrin and Langlois, and others, while, as shown below, compensation through supernumerary organs undoubtedly occurs. The opposite condition to hypertrophy—atrophy—may, on the other hand, bring the adrenals to the brink of total physiological insufficiency, and thus induce bronzing. But under these circumstances the quality of the secretion may also play an important rôle in the production of this symptom, the causative condition—impaired nutrition—being of a nature suggesting such an effect. As the bronzing progresses with the advance of the atrophic process, it may appear long before the severe symptoms of suprarenal insufficiency assert themselves. This type is well illustrated by a case described by Carlin Philips,[16] in which bronzing began fourteen years before the onset of the profound constitutional symptoms. Rolleston[17] has emphasized the fact that atrophy of the adrenals occurs normally in old age, and that it may occur earlier in life and give rise to Addison's disease.

Total absence of the adrenals has been observed in autop-

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[14] Oestreich: Zeitsch. f. klin. Med., Nos. 1 and 2, 1896.
[15] Stilling: Virchow's Archiv, Dec., 1889.
[16] Carlin Philips: Journal of Experimental Medicine, vol. iv, 1900.
[17] Rolleston: Lancet, Mar. 23, 1895.

sies of cases of Addison's disease. In Rispal's[18] case, notwithstanding the presence of typical symptoms, including bronzing, there was no evidence of tuberculosis, the abdominal sympathetics were normal, and there was no evidence to show that the adrenals had ever existed. He was only able to find two similar instances in literature. In animals compensation occurs in various ways. In four rats which survived bilateral adrenalectomy several months Boinet found three or four reddish organs round the kidneys structurally similar to the cortex of adrenals. He found the spleen enlarged and that its removal rapidly caused death, thus strongly suggesting vicarious function. Auld observed very great hypertrophy of the thymus after one capsule had been removed two or three months. In the human being accessory suprarenal bodies have been found in the semilunar ganglion and in the midst of the solar plexus by Jaboulay[19] and by Stilling.[20] Gottschalk[21] found accessory adrenals in the infundibulo-pelvic ligament close to one of the ovaries. Rossa,[22] in reporting a similar instance, alluded to other well-authenticated cases. Wiesel[23] examined fifteen pairs of testicles and epididymes from the newborn and found accessory suprarenal capsules connected with them 23 times: 5 times on each side and 13 times singly. The accessory organs had the same structure that the gland usually shows. They were usually situated in the connective tissue about the vas deferens, and were surrounded by a mass of blood-vessels. In older children or adults no fully developed accessory glands were found, but there were remnants in the form of strings and clumps of cells. Aichel,[24] on the other hand, emphasizes the importance of organs found by Marchand near the testes in man and in the broad ligaments of woman, which organs are homologous to the suprarenal bodies. These few examples could be greatly multiplied were they not sufficient to show that total absence, or complete, but slow, destruction of the

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[18] Rispal: Le Progrès Médical, Aug. 29, 1896.
[19] Jaboulay: Lyon Médical, Nov. 2, 1890.
[20] Stilling: Revue de Médecine, Oct., 1891.
[21] Gottschalk: Centralblatt für Gynäkol., No. 15, 1898.
[22] Rossa: Centralblatt für Gynäkol., No. 25, 1897.
[23] Wiesel: Wiener klin. Wochenschrift, May 5, 1898.
[24] Aichel: Münchener med. Wochenschrift, Sept. 4, 1900.

organs, may not in some instances prove fatal, and that the physiological functions of the adrenals can be fulfilled vicariously.

Addison's disease with absence of adrenals only shows that the compensation established was insufficient to carry the subject through normal life. Nothnagel's inability to observe pigmentation in 153 animals from which he had removed both adrenals is often quoted to show that these organs are not directly connected with this symptom. But death in all these animals occurred long before bronzing could have appeared. Boinet, on the other hand, who utilized animals in which compensatory organs are often found, observed typical pigmentation in all animals that had lived several months after bilateral adrenalectomy. Tizzoni noted the same results after crushing the organs. Various investigators, beginning with Brown-Séquard, had already noted that pigmentation appeared in animals in which the operation did not prove fatal for some months, the symptoms present being analogous to those of Addison's disease.

On the whole, there appears to be good ground for the belief that:—

1. Addison's disease is a symptom-complex due to insufficiency of the adrenals.

2. Insufficiency of the adrenals only manifests itself by bronzing when, from any cause, all but a small proportion of the organs has been rendered physiologically inactive. Hence,

3. Bronzing is a symptom of advanced adrenal insufficiency brought on by any local, peripheral, or general disease.

Its appearance depends upon the *quantity* of *normal* substance, whether this occupy a small area in one organ or be disseminated amidst morbid foci, in one or both of them.

But *how* does the pigmentation originate, and *why* does advanced insufficiency of the adrenals give rise to it? The relation between this terminal stage and pigmentation is evident, while the occurrence of the latter imposes the conclusion that the suprarenal secretion must serve to keep the pigment within its precincts: the red corpuscle. We may ascertain this by locating the seat of dissociation: *i.e.*, the spot where the absence of secretion causes the pigment to leave the corpuscle

or fail to be taken up by it. We already have reason to believe that this occurs in the lungs, and, hæmoglobin being the predominating factor in this connection, analysis of the conditions that compromise the integrity of the hæmoglobin molecule in the lungs will doubtless furnish some clue to the nature of the process involved.

THE ADRENALS IN THEIR RELATION TO CHLOROSIS.

Hæmoglobin not only requires iron for its elaboration, but this metal constitutes by far its most striking characteristic. It cannot be formed without iron any more than the chlorophyl of plants can be formed without it. Again, since the power of hæmoglobin to take up oxygen depends upon the proportion of this ingredient, a sufficiently great ratio both of iron and of the pigments with which it enters into association must be present to insure normal functions, all other features of the process being adequately carried out. The almost unfailing beneficial effects of iron in chlorosis are well known. We are led to believe, therefore, that chlorosis is mainly due to a deficiency in the quantity of iron taken into the organism or to the imperfect assimilation from animal foods, etc.

Yet there are many phenomena of chlorosis that are not satisfactorily accounted for and which the known physiological properties of the suprarenal secretion seem to readily explain. Thus, the gastric symptoms, so marked in practically all cases, are easily understood when the effects of suprarenal extract on muscular tissue are recalled. Moreover, the close relationship between the first artery of the cœliac axis and the stomach, on the one hand, and the origin of the cœliac axis from the aorta —which contains freshly adrenalized blood—on the other, all previously referred to, show how direct is the connection between the adrenal secretion and the gastric muscular walls. What is more clearly accounted for by this physio-anatomical distribution than the gastric dilation and gastroptosis constantly observed in these cases: *i.e.*, when relaxation of the *muscular* walls, due to deficiency of suprarenal secretion, is introduced as a cause? That in *all* other diseases in which suprarenal *insufficiency* prevails gastric disorders are more or less marked further confirms this fact. Again, the cardiac

murmurs and venous hums that are practically always observed represent a striking feature of chlorosis. That they are functional cannot be denied, since they usually cease when the blood's hæmoglobin shows an increase, as noted by Richardson[25] and others. That muscular relaxation of the cardiac walls exists can also be shown. In a careful examination of 22 hearts Gautier[26] found 20 enlarged; this organ, as we have seen, is the first to receive perfect blood from the lungs directly from the aorta through the coronaries; is it not plain that deficiency of suprarenal secretion also causes muscular relaxation of this organ? The lassitude and indisposition to exertion are obviously of muscular origin and traceable to the same cause. When we come to the most striking symptom of chlorosis, the extreme pallor, suprarenal insufficiency again suggests itself, since we not only have the blood-changes to account for it, but also the contraction of the capillaries of the surface caused by the simultaneous dilation of the abdominal vascular trunks which the reduction of adrenal secretion involves. The applicability of the postulate—"Vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation"—in this connection seems to us to greatly strengthen the position taken.

A review of the literature upon the absorption of iron and particularly that bearing upon its *intra vitam* relations with hæmoglobin soon shows the correctness of Prof. H. C. Wood's[27] remark that, "although a great amount of work has been done by chemists upon the absorption and elimination of iron, the results have been so imperfect, contradictory, and difficult of explanation that they are at present of very little use to the clinician." Bunge's view that iron is not absorbed has steadily lost ground, and there is considerable available evidence to show that absorption occurs. A. B. Macallum,[28] for instance, observed, in sections of intestines taken from animals first starved then fed upon a substance containing albuminate of iron, free leucocytes crowded with granules of iron

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[25] Richardson: Lancet, June 27, 1891.
[26] Gautier: Deutsch Archiv f. klin. Med., Bd. lxii, H. 1 and 2, 1899.
[27] H. C. Wood: *Loc. cit.*
[28] A. B. Macallum: Jour. of Physiol., vol. xvi, 1894.

pigments in the intestine, some appearing to pass out through the epithelial cells, while others advanced into the subepithelial elements. He also found them in the venules of the villi, the capillaries of the liver, the spleen, etc.

If the question of *absorption* is still *sub judice,* what can we say of the process through which iron combines with other bodies to form hæmoglobin? Yet there are general points of a chemical nature which may assist us in determining the gross lines of this process. Thus we know that when hæmoglobin is acted upon by acids in the presence of oxygen hæmatin is formed; and also that in the *absence* of oxygen a *hæmochromogen* first appears which *slowly loses its iron,* the end-product being *hæmatoporphyrin.* In chlorosis the tissues probably play in this connection the part of the acid usually employed in laboratories to disintegrate hæmoglobin: *they abstract oxygen.* The imperfect condition of the blood involving reduced oxidation, oxyhæmoglobin is not always formed, and arterial blood fresh from the lungs, while still containing a large proportion of this compound,—though just sufficient, in some cases, to insure continuation of the vital processes,—also contains a more or less great proportion of reduced hæmoglobin. Under these conditions the avidity of the tissues for oxygen causes them not only to absorb the one molecule of this gas from the oxyhæmoglobin, but also to make up for the deficiency by taking up oxygen from hæmoglobin: *i.e.,* the only remaining source of supply. We thus have in the blood the precise conditions required for the reaction outlined, namely: absence of oxygen and a powerful deoxidizant, and therefore obtain as end-results free iron and hæmatoporphyrin. But does free hæmatoporphyrin appear in the blood when insufficiency of the adrenals occurs? The urine alone can afford the desired information, and the inquiry must therefore be turned in this direction.

Hæmatoporphyrin was found in small quantities in normal urine and practically always in pathological urine by Garrod[29] and Stockvis,[30] while various authors, including MacMunn,[31]

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[29] Garrod: Journal of Physiology, vol. xvii, No. 5.
[30] Stockvis: Jahresb. f. Therap. Chemie, vol. xxiii, 1893.
[31] MacMunn: Journal of Physiology, vol., 1885.

D. Fraser Harris,[32] Nakarai,[33] and Ogden[34] have collectively found it in rheumatic fever, pericarditis, peritonitis, meningitis, cirrhosis of the liver, croupous pneumonia, typhoid fever, measles, Hodgkin's disease, exophthalmic goiter, pulmonary tuberculosis, pleurisy, leprosy, lead poisoning, and chronic poisoning with sulphonal, trional, and tetronal.

Another important feature of these reports is that they also refer to the discovery of hæmatoporphyrin in several cases of Addison's disease, while D. Fraser Harris[35] alludes to a case of exophthalmic goiter attended with hæmatoporphyrinuria in which "some patchy pigmentation of the skin with bullæ filled with red, alkaline fluid" had been observed. Still another point of association with suprarenal insufficiency is furnished by several reported cases of peritoneal blood-effusion. If we recall the various instances of suprarenal apoplexy (Arnaud), followed by rupture of the organs previously alluded to, the presence of adrenal disease can be surmised. Again, Stokvis found that sulphonal caused punctiform hæmorrhages into the mucous membrane of the stomach and intestines, besides hæmatoporphyrinuria, in rabbits. Capillary centrifugal dilation, due to the protective overactivity of the adrenals, which *precedes* insufficiency, and consequent constriction of the abdominal trunks had obviously appeared: the counterpart of other experiments already related in which hæmaturia, epistaxis, etc., had been noticed after injections of suprarenal extract.

As to the hæmoglobin ratio in these cases, the sequence of chemical reactions involved in the morbid process suggest that a reduction should simultaneously appear. D. Fraser Harris[36] refers to a case reported by Cant in which the ratio was 40 per cent. of normal with 2,250,000 red corpuscles—evidently a case in which hæmogenesis was impaired. A case of McCall Anderson's, on the other hand, showed a normal number of red corpuscles, while the hæmoglobin was only 60 per cent. of normal. In a case referred to in Campbell's paper (Oswald's),

[32] D. Fraser Harris: British Medical Journal, Feb. 5, 1898.
[33] Nakarai: Deutsches Archiv f. klin. Med., Nos. 2 and 3, 1897.
[34] Ogden: Boston Med. and Surg. Jour., Feb. 24, 1898.
[35] D. Fraser Harris: *Loc. cit.*
[36] *Ibid.*

the percentage of hæmoglobin was 49 per cent. We have seen the close association between hæmoglobinuria and suprarenal insufficiency; it is probable that we have in hæmatoporphyrinuria, therefore, an advanced step in blood-disintegration connected with correspondingly advanced suprarenal disease bordering on total insufficiency. This view is sustained by the practically general prognostic estimate of clinicians. Referring, for example, to McCall Anderson's case, in which hæmatoporphyrinuria had recurred for years, the man being still living, Harris says: "Had I not seen Prof. McCall Anderson's case . . . I should say this red urohæmatoporphyrinuria was a most grave symptom, a precursor of a fatal issue; such, at any rate, it seems to be in the case of women."

A direct connection between hæmatoporphyrinuria and suprarenal insufficiency further asserts itself when the symptomatology of cases in which the former occurs are studied from this standpoint, and the morbid lesions are carefully sought post-mortem. A case of hæmatoporphyrinuria ably described by Keith Campbell,[37] of Perth, is especially valuable in this connection. The abdominal pain, muscular paresis beginning at the extremities and including the diaphragm, tendency to diarrhœa, Cheyne-Stokes respiration, convulsions, and coma interspersed among the symptoms of the major disease (mania and pulmonary tuberculosis) typify the phase of overactivity bordering on insufficiency which corresponds with the sequence of events in the chemical reactions referred to above. The most striking feature of this case, however, is the fact that by far the most marked lesions found post-mortem were in the adrenals. The report of the pathologist, Dr. W. F. Robertson, in this connection was as follows: "Right adrenal shows in the cortex numerous large areas in which the epithelial cells have undergone a marked degenerative change, consisting of the replacement of the protoplasm by clear globules. These globules, which vary considerably in size, do not (with an occasional exception) give a fatty reaction with osmic acid. There is no evidence of any tubercular disease in any part of the organ. Left adrenal shows similar changes. There is no

[37] Keith Campbell: Journal of Mental Science, April, 1898.

tubercular disease. The degenerative changes above noted are evidently the same as those that are so commonly to be observed in the adrenal epithelium in various diseases." This is probably the only case of hæmatoporphyrinuria in literature in which the adrenals were carefully examined. That advanced disease of these organs existed in others is shown by the frequency of references to hæmorrhage and intraperitoneal blood-effusions associated with morbid phenomena distinctly of suprarenal origin.

The last point to be determined is the relationship between the hæmatoporphyrin obtained in laboratories from hæmoglobin and that found in the urine. This may be ascertained spectroscopically. D. Fraser Harris refers to the laboratory pigment as follows: "The acid solution is two-banded, and very characteristic; the pigment is iron-free." If we now compare this with the spectroscopic findings of a case of hæmatoporphyrinuria studied by J. B. Ogden[38] the identity of both laboratory and pathological pigments will appear. "The dark urine which was collected on February 12th was examined with the spectroscope. At first the untreated urine (acid) was used, but with unsatisfactory results, since the two spectral bands of each hæmatoporphyrin could not be made out with certainty. The pigment was then separated from the urine by Salkowski's method and it was found that both the acid and alkaline solutions gave the characteristic absorption-bands of hæmatoporphyrin." It is thus shown that the hæmatoporphyrin artificially produced and hæmatoporphyrin of pathological origin are identically the same.

What becomes of the free iron? The elimination of this metal by the urine has been demonstrated by Kobert and his assistants, Damaskin, Kumberg, Busch, and Steuder,[39] who ascertained that, while the daily elimination in the urine was hardly 1 milligramme in diseases attended by destruction of the blood, this elimination not only increased, but the presence of biliary coloring matter in the urine bore no influence upon this increase. Various authors have demonstrated that it was eliminated in great part by the intestinal tract, the

[38] J. B. Ogden: *Loc. cit.*
[39] Quoted by H. C. Wood, *loc. cit.*

liver, kidneys, etc., also assisting, while Macallum,[40] Kunkel,[41] Quincke,[42] Hall,[43] Hare,[44] and others have traced it to the blood of various organs after feeding animals upon iron-containing substances. An interesting view in this connection is that of Hall, whose researches tend to show that the iron of the organism occurs both in fixed combination—*i.e.*, in hæmoglobin—and in very loose organic combination, the latter varying constantly with the amount of iron ingested. This would coincide with the conceptions herein submitted, since they suggest the existence of a fixed ratio of hæmoglobin and therefore of iron, and the onset of disease as soon as the fixed combination, hæmoglobin, is structurally compromised.

A striking association with the suprarenal functions also appears when the disposal of iron is analyzed. The occurrence of bronze spots in connection with various infections and intoxications, tuberculosis, syphilis, arsenic poisoning, etc., has already been referred to, the development of this *melanoderma* occurring in response to a multitude of abnormal factors. The bronzing of Addison's disease is due, as is well known, to a *melanin*, a pigment *which contains no iron*, found around the vessels, and a product of cellular catabolism. Again, the hair is a recognized depository for eliminated iron; and deeply-pigmented hair is a characteristic of Addison's disease. We thus have tangible proof that Addison's disease, the typical manifestation of suprarenal insufficiency, is attended with hæmoglobin disintegration, and we have seen the close relationship between this disease and chlorosis.

But why is chlorosis not also attended with bronzing besides the other symptoms of Addison's disease discernible? As previously stated, chlorosis is herein considered as a stage of suprarenal insufficiency, not necessarily organic nor pathologically connected with Addison's disease. It is attributed in most cases to physiological incompetence of the adrenals, whether this be due to inadequate development or to impaired nutrition. Yet, the accumulation of free pigment must be

[40] Macallum: *Loc. cit.*
[41] Kunkel: Archiv für d. Gesam. Physiol., lxi.
[42] Quincke: Archiv für exp. Pathol., Bd. xxxvii, 1896.
[43] Hall: Archiv f. Anatomie u. Physiol., 1896.
[44] Hare: Archiv für Verdauungs Krank., vol., 1898.

accounted for, and, if the cutaneous tissues do not show pigmentation,—which they sometimes do; witness the cases reported by Bouchard and Ponzet[45] and perhaps the yellowish-amber pigment of alkaline hæmatoporphyrinuria,—that pigment should be present elsewhere, at least in some cases, since the urine of chlorotics is usually pale, though copious. We have ample evidence that some unaccounted-for substance accumulates in the blood of chlorotics, in the frequency of thrombosis as observed in these cases. The researches of Leichtenstein[46] have shown that thrombi can occur in practically any part of the organism, but particularly in the lower extremities (phlegmasia alba dolens) and the cerebral sinuses. Review of the literature on this subject soon shows that the nature of these thrombi has remained unascertained and the "peculiar yellowish-green" pigmentation of the skin likewise. Stengel,[47] alluding to the latter, says: "The pigment is doubtless altered hæmoglobin, but its exact nature is unknown." That *acid hæmatoporphyrin* is the basis of all these forms of pigmentation seems to us probable. In the blood of chlorotics this may (but *secondarily*, owing to alkaline surroundings) be transformed into *alkaline hæmatoporphyrin*, and this yellowish or amber pigment account for the peculiar hue of the skin. In Addison's disease a *melanin*—probably a derivative of hæmoglobin, but a more stable pigment, owing to its probable absorption into tissues and deposition as a catabolic product into the melanoblasts—accounts for the bronzing.

But how and why is chlorosis so frequently cured with iron? Chlorotics do not always recover under the administration of iron, and other agencies hygienic and medicinal will sometimes bring on cure where iron has failed. We are therefore not dealing with a disease invariably associated with a quantitative deficiency of this metal, but one in which it is not properly assimilated. Its effects must, therefore, be indirect and be addressed mainly, at first, to hæmatogenic functions, provided the gastro-intestinal tract does not by inadequacy too greatly limit absorption. An increase of red blood-

[45] Bouchard and Ponzet: Trans. Ninth Inter. Congress, 1888.
[46] Leichtenstein: Münchener med. Wochenschrift, 1899.
[47] Stengel: "Text-book of Pathology," edition, 1900.

corpuscles first occurs, and, according to Osler[48]: "In some instances the globular richness rises above normal." The adrenals—which, as we have seen, are merely physiologically deficient (in most cases), through impaired nutrition, their protoplasm failing to receive from the imperfect blood coursing through them sufficient elements for the creation of a perfect secretion or enough of it—soon increase their activity. Better nourished, their secretion improves in quantity and power and more iron is assimilated and fixed in the formation of hæmoglobin: a phase of improvement which, of course, requires some time. "The increase of hæmoglobin," says Osler, "is slower, and the maximum percentage may not be reached for a long time." Arsenic also cures some cases; this agent is particularly active as a suprarenal stimulant and the symptoms following a poisonous dose are those of cholera: *i.e.*, those following removal of both adrenals. As regards iron, V. H. Meyers and F. Williams[49] state that "both frogs and mammals are killed by it, the symptoms in warm-blooded animals being vomiting, purging, great fall of blood-pressure, muscular weakness, and finally coma and death." A more clearly defined list of the effects of double adrenalectomy could not be presented. Hence, iron must directly stimulate the adrenals in chlorosis in addition to its rôle as a structural constituent of the hæmoglobin-molecule.

THE ADRENALS IN THEIR RELATION TO BLOOD-DISINTEGRATION UNDER THE INFLUENCE OF POISONS.

Hæmaturia—*i.e.*, the presence of blood in the urine—follows injections of suprarenal extract, and therefore typifies overactivity of the adrenals. The experiments of Swale Vincent, among others, have demonstrated the effects of suprarenal-extract injections in this connection, "blood-colored urine" and "bleeding from the mouth and nostrils" in guinea-pigs and rats having been produced by this agent. These fully illustrate the influence of pressure in the capillaries brought on by contraction of the central vascular trunks.

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[48] Osler: "Practice of Medicine," p. 801.

[49] V. H. Meyers and F. Williams: Archiv für Exper. Path. u. Pharm., Bd. xiii, 1876; quoted by Wood, p. 418.

Hæmoglobinuria, with which hæmaturia is frequently confounded, is an entirely different condition. Referring to the former disorder, Osler[50] says: "The essential pathology of the disease is unknown, and it is difficult to form a theory which will meet all the facts. . . . Increased hæmolysis and solution of the hæmoglobin in the blood-serum (hæmoglobinæmia) precedes, in each instance, the appearance of the coloring matter in the urine." Again: "The coloring matter is not hæmatin . . . nor in reality always hæmoglobin, but it is most frequently methæmoglobin. The urine has a red or brownish-red, sometimes quite black, color, and usually deposits a very heavy brownish sediment." That the identity of hæmoglobinuria is also a source of confusion is fully emphasized by the author. Indeed, from what has been said of bronzing—and if our views are sound—the true source of what is often termed "hæmaturia" or "hæmoglobinuria" is, in truth, methæmoglobin or its isomer hæmatin, a decomposition product of hæmoglobin, which we primarily attribute to suprarenal insufficiency. Briefly, while hæmaturia indicates overactivity of the adrenals, hæmoglobinuria, methæmoglobinuria, and, we will add, hæmatoporphyrinuria, typify, in our opinion, the three downward steps of suprarenal insufficiency as manifested in the blood. That all these phenomena appear in the same order in the symptomatology of poisons—the degree of blood-disintegration increasing with the virulence of the toxic substance which enters the blood—will now be shown.

Weir Mitchell long ago observed that, when death came on *rapidly* after a rattlesnake-bite, the blood-corpuscles remained intact. This is fully sustained by the need of a certain time for the disintegration of blood through suprarenal insufficiency. Weir Mitchell also noted that, in cases in which the venom did not act promptly, the corpuscles appeared altered, some being dentated: one of the signs of impending disintegration. This constitutes, in all probability, the primary result of suprarenal insufficiency. With Reichert, he subsequently ascertained that the corpuscles became spherical. Brainard[51] had also noticed that they became spherical and

[50] Osler: "Practice of Medicine," p. 854, edition of 1898.
[51] Brainard: Académie des Sciences, Nov. 28, 1853.

that the leucocytes tended to form masses. Albertoni[52] found that alteration of color was the main change observable in the red corpuscles, their coloring having passed into the plasma, which had become reddish. The leucocytes appeared to form broad plaques. A study of this blood showed that its corpuscles became *easily disintegrated;* far more so than under usual conditions. Vulpian[53] ascertained that the blood-corpuscles were almost all deprived of their hæmoglobin when death did not occur early.[54] Camus and Gley[55] found the serum intensely red: a feature which they attribute to a great quantity of dissolved hæmoglobin.

Among the blood-disintegrating poisons, acetanilid (antifebrin) comes first in alphabetical order. This drug was found by Herczel, when given to dogs for a length of time, to *reduce the alkalinity of the blood,* the serum being also found to contain "dissolved coloring matter": a fact which probably accounts for the inability of blood from poisoned subjects to adhere in rouleaux. Lépine and Aubert[56] furthermore observed that the oxygen of the blood was distinctly decreased. The effects of aconite or aconitine upon the blood are not studied in Wood's work; yet a foot-note refers to subpleural ecchymoses, an indication of advanced hæmolysis, observed in animals by Laborde and Duquesnel, and caused by toxic doses of aconitine. In antimony poisoning the viscera are intensely congested. Magendre found the lungs studded with hepatized areas. Ackermann observed marginal emphysema with spots of atelectasis. The blood is stated by Wood to "usually coagulate imperfectly." Alcohol was found by Jaillet and Hayem to produce in animals "extensive alteration in the blood-corpuscles, many of these bodies being shriveled and altered in form, with yellow precipitates of hæmoglobin in their interior." Arsenic was found by Bettmann[57] to cause a marked lessening in the number of red blood-corpuscles and the percentage of hæmoglobin. Wood, in this connection, notes the interesting

[52] Albertoni: Lo Sperimentale, Aug., 1879.
[53] Vulpian: Académie des Sciences, March 6, 1882.
[54] Quoted by Noé, *loc. cit.*
[55] Camus and Gley: Académie des Sciences, Jan. 31, 1898.
[56] Lépine and Aubert: Gazette Médicale de Strasbourg, i, 1887.
[57] Bettmann: Beiträge zur Path. Anat., etc., xxiii.

fact that arsenic, antimony, phosphorus, and ammonia act very similarly, if not identically, upon the blood. He also refers to the *bronze* pigmentation "which is almost pathognomonic of chronic arsenicalism."

The bromides were found by H. Bill to produce "a very decided decrease in the amount of carbonic acid thrown off from the lungs. . . . On the other hand, the quantity of urine was usually increased, and the coloring matters invariably augmented." The blood-conditions of camphor are not referred to, but Professor Wood alludes to a case in which a drachm of chloral-camphor swallowed by mistake produced very severe prostration, feebleness of the pulse, vomiting, fifteen coffee-ground stools, etc. In carbolic-acid poisoning, according to the same observer, "the liver, spleen, kidneys, and, indeed, all the organs are found filled with dark, imperfectly-coagulated blood, such as is habitually found after death from asphyxia." The inference that the oxygen of the blood must have been markedly decreased during life is worthy of note. The urine is likewise bloody. Chloral was thought by Richardson[58] to cause the blood to coagulate less firmly than when the latter is normal. Vulpian noted that it gave rise to hæmaturia when injected hypodermically, this phenomenon being markedly increased when the drug was injected into the veins.

Chloroform was found by Harley[59] to render the blood very liquid and to give a bright, arterial hue. After a time crystals of oxyhæmoglobin form in it. Boettcher,[60] Schmidt, and Schweiger-Seidel[61] observed that the blood-disks diminished in size; but these effects were noted *in vitro*, and are therefore of no value to us. Wood refers to the very sensitive test of the destruction of the red corpuscles in the body which the presence of icterus affords, and states that the observation of Frerichs that it does occur, though rarely after chloroformization, is correct. In digitalis chronic poisoning ecchymosis of the gastro-intestinal mucous membrane, the meaning of

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[58] Richardson: Medical Times and Gazette, Sept. 4, 1870.

[59] Harley: Proceed. Physiol. Society of London, 1865.

[60] Boettcher: Virchow's Archiv, xxxii, 126.

[61] Schweiger-Seidel: Bericht. d. Königl. sachs. Gesell. de Wissensch. math.-phys. Kl., 190, 1867.

which has already been referred to, has been noted by Köhnhorn.[62]

Hydrocyanic acid causes the blood to assume a dark, venous hue. Wood refers to Gaethgens, who found that the blood of the first stage of poisoning clearly showed the absorption bands of oxyhæmoglobin under the spectroscope, while Preyer demonstrated that "the dark blood of the advanced stage gives only the lines of reduced hæmoglobin." In truth, this poison is the most violent of the pharmacopœia and the more advanced stages of blood-disintegration would doubtless occur were the victim to live long enough. Mercury is stated to cause the blood to suffer very decidedly, becoming fluid and having its power of coagulation impaired. Wright found its solid constituents notably diminished, including albumin, fibrin, and the red corpuscles, and noted that it contained a quantity of fœtid fatty material. In bichloride poisoning the urine is sometimes bloody. Physostigmine poisoning, according to Fraser, causes the blood after death to coagulate slowly and loosely, the red corpuscles presenting various irregularities in outline. The blood of animals killed with quinine was found by Bonome and Arverdi, Magendie, Monneret, Melier, and Baldwin to be dark, defibrinated, fluid, and incapable of forming a clot. Briquet and Hare, who observed that this alteration was not constant, probably used smaller doses.

The next step in the process of hæmolysis is the formation of *methæmoglobin*, which gives the blood a chocolate or dirty-brown color, as shown by Gamgee. Free hæmoglobin was found by Hayem to be more sensitive than corpuscular hæmoglobin to methæmoglobinizing substances; and as Pugliese observed that the normal temperature of the body, 37° C., favored hæmoglobinization, the conclusion of Carreau that an acute methæmoglobinæmia represents the stage of blood-disintegration brought on by snake-venoms seems warranted. This author[63] states that the Martinique viper *(fer de lance)* causes the blood to become very dark—almost black—"*prune-juice* like," to use his words. That methæmoglobin was present in abundance was proven spectroscopically. Pugliese has also

[62] Köhnhorn: Lancet, i, 583, 1876.
[63] Carreau: Semaine Médicale, vol., 1893.

determined[64] that venoms first cause alteration of the corpuscles, and that the freed hæmoglobin is then disintegrated.

Ammonium picrate was found by Erb to cause the blood of animals to assume a dirty-brown color. Nitroglycerin and amyl nitrite are referred to as acting alike. Nitrite of amyl causes the blood to become chocolate colored. Gamgee found that under these conditions the spectrum bands of oxyhæmoglobin disappeared, and were replaced by bands almost similar to those of acid hæmatin. Methæmoglobin is thought by MacMunn to be a mixture of hæmatin and soluble albumin.[65] The blood had also lost its power to absorb oxygen. Wood remarks in this connection: "The accord of the results of this chemical investigation with those arrived at by a purely physiological study of the drug is very striking and very beautiful, both teaching the same thing—*lessened,* but not absolutely arrested, *oxidation.*"

Copper, in toxic doses, has been found to be attended, according to Wood, with black urine, due to the presence of hæmoglobin without unaltered blood-corpuscles. He also states that "after death alterations of the blood and wide-spread fatty degeneration have been noted by numerous observers." Zinc poisoning is referred to as giving rise to the same symptoms as the corresponding salts of copper. Phenacetin is also stated to be followed, when given in large doses, "by general cyanosis and discoloration of the blood, due to the formation of methæmoglobin." In phosphorus poisoning the blood is stated to be "often profoundly affected, becoming very dark, losing its power of coagulation, and apparently suffering also in its corpuscular elements, for ecchymoses are almost universal and hæmatin crystals are occasionally found in the viscera. . . . Silbermann[66] states that thrombi are found in the blood-vessels."

In potassium-chlorate poisoning the urine, according to Wood, is "often of an opaque reddish-brown or blackish color . . . frequently containing the *detritus* of blood-corpuscles. Hæmoglobinuria has been noticed, and methæmoglobin is a

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[64] Pugliese: Archives Italiennes de Biologie, 1895.
[65] MacMunn: "The Spectroscope in Medicine," 100, 1881.
[66] Silbermann: Virchow's Archiv, cxvii, 1889.

common constituent. . . . The blood is usually chocolate colored . . . the liver and spleen are enlarged and filled with the brownish *débris* of red blood-corpuscles; the bone-marrow and the brain are often similarly colored. . . . The changes in the blood are the result of the formation of a substance apparently identical with the methæmoglobin of Hoppe-Seyler and characterized by the appearance in its spectrum of a dark line in the red. . . . That it is produced in the body during life," continues Wood, "has been proved in cats, dogs, and rabbits by A. Falck,[67] by H. Lenhartz,[68] and by Cahn,[69] and is also shown in man by the wide-spread staining not only of the interior of the blood-vessels, but also of the walls of the whole lymphatic system, found after death from the chlorate." In antipyrin poisoning H. M. Briggs[70] observed "blackish urine, with albumin and blood-corpuscles." The peculiar lividity often seen in persons under the influence of antipyrin "is probably due to changes in the blood itself," writes Wood. "According to Lépine, methæmoglobin is largely formed during [antipyrin] poisoning." That other authors failed to detect it is accounted for by the fact that the doses of antipyrin used in their experiments were inferior to those employed by Lépine.

The last stage of blood-disintegration, indicated by the presence of *hæmatoporphyrin*, and which corresponds with the bronzing stage of Addison's disease as regards the degree of suprarenal insufficiency, has only been observed so far in connection with few toxics. In chronic sulphonal poisoning, which is stated to have been fatal in seventeen cases out of twenty, the first symptom is hæmatoporphyrinuria. "The explanation of the occurrence of hæmatoporphyrinuria is at present very difficult," says Professor Wood; "frequently it does not come until several days after the ingestion of the last dose." He refers to the case of Franz Müllen, in which the hæmoglobin fell during the period of red urine to 45 per cent., returning with convalescence to 85 per cent.; and also to

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[67] A. Falck: Archiv für d. gesam. Physiol. des Menschen u. der Thiere, 1889.
[68] H. Lenhartz: Beiträge zur Path. Anat., etc., Festschrift, 1887.
[69] Cahn: Archiv für exper. Path. u. Pharm., xxiv, 1887.
[70] H. M. Briggs: London Med. Recorder, March, 1891.

Hoppe-Seyler's belief that "the anatomical changes in sulphonal poisoning are really secondary to the destruction of the red blood-disks." Trional poisoning is also stated to be attended with hæmatoporphyrinuria, though to a less pronounced degree. Santonin is stated to sometimes give the urine a purplish-red color. Oxalic acid was also found by Rabuteau to cause the blood to become "everywhere scarlet." Taylor[71] did not, according to Wood, observe this phenomenon in all cases: a discrepancy easily accounted for by differences in the quantity of poison taken.

The toxic agents analyzed in Wood's "Therapeutics" represent all those in which references to blood-changes have been made, and we thus have ample evidence that all agents capable of acting as toxics may give rise to disintegration of the blood similar to those which were herein described as being of suprarenal origin. The following postulates, therefore, appear to us to rest upon a firm foundation:—

1. The adrenals are stimulated or functionally depressed by venoms or poisons according to the dose introduced into the circulation.

2. Variations in the functional activity of the adrenals induce corresponding variations in the mutual affinity of the bodies entering into the hæmoglobin-molecule.

INSUFFICIENCY OF THE ADRENALS AS A SOURCE OF BLOOD-DISINTEGRATION.

Methæmoglobin. — Gamgee has shown that lessened oxidation coincides, when sufficiently advanced, with the disappearance of the spectrum bands of oxyhæmoglobin, and that these are replaced by others—practically those of acid hæmatin —which give the blood the chocolate color assumed by it in the earlier stages of hæmoglobin-disintegration. Wood says, referring to this acid hæmatin: "Recent researches have demonstrated that the spectrum of this new compound is identical with that of the methæmoglobin of Hoppe-Seyler."[72] That this methæmoglobin represents an early stage of hæmoglobin-disintegration is evident from the fact that Gamgee "showed

[71] Taylor: "Medical Jurisprudence," i, 224.

[72] Hoppe-Seyler: Zeitschrift f. Prak. Chemie, vols. ii and iii.

conclusively that this new compound yields its oxygen to reducing agents": a point which we must here emphasize. Further, Gamgee found that, when, after nitrite poisoning, this chocolate blood appeared, it still ozonized prepared guaiacum-paper, though not so actively as under normal conditions. "Evidently then," says Professor Wood, "absorption of oxygen must take place; evidently the blood-corpuscles must perform their respiratory function; but evidently also *they are greatly crippled and impaired in the rapidity and ease of its performance.* Hæmic respiration is, in other words, greatly interfered with, but not abolished."

We have already seen that chemistry and physiology have both established these facts. The deduction that methæmoglobin is a product of early blood-disintegration therefore is solidly supported. An important question, however, demands elucidation: What is the nature of the process? In other words, *how* and through what process is methæmoglobin formed in the organism after poisoning?

The respiratory symptoms are stated by Lauder Brunton and Fayrer[73] to be the most marked witnessed after snake-bites in India. Wall[74] states that a strong dose of cobra-venom causes almost instantaneous arrest of respiration; a weaker dose slows it, and asphyxic symptoms follow. Viper-venom was found by Phisalix to markedly affect the respiratory functions. It first produced excitement, with "accelerated respiration," then "somnolence, with slowing of respiration." We have here distinct evidence of reduced oxidation and accumulation of carbonic acid. The next step is illustrated by Carreau's already-quoted observation that the Martinique *fer-de-lance* viper caused the blood to become very dark, "*prune-juice* like"; the presence of a large proportion of methæmoglobin had been established spectroscopically. Even bee-venom, in sufficient quantity, gives rise to marked dyspnœa and "black blood," as observed by Paul Bert.

As previously shown, several drugs have been sufficiently studied in this connection by investigators to indicate that methæmoglobinuria occurs after the ingestion of poisonous

[73] Lauder Brunton and Fayrer: Proceed. Royal Society, 1874.
[74] Wall: Quoted by Noé, iii, p. 368.

doses of these drugs. Nitroglycerin and amyl nitrite have both been found to act similarly, in many ways, by Lauder Brunton, Tait, Murrell, Hay, and Hénocque. As the latter drug is the more completely reviewed by Wood, it will be used as the basis of this inquiry. "When," says this author, "an animal inhales amyl nitrite, the arterial and venous blood soon become of a nearly uniform hue, which resembles somewhat that of normal venous blood, but is quite distinct from it, having a chocolate tint." Are we dealing with mere deficiency of oxidation or accumulation of carbonic acid? Evidently not, since Wood states that "this chocolate-colored blood *does not assume the arterial hue when shaken up with the air.*" According to Gamgee, the nerve-centers are directly affected; but we have already ascertained that the respiratory centers are not the source of phenomena that occur in this connection, and, as shown below, the effects of the toxic occur notwithstanding division of the spinal cord. As the splanchnic nerve is that connected with the adrenals, the sympathetic system must be the one morbidly influenced by the poison. An important fact suggested by this nervous origin, however, is that the direct hæmolytic influence of the poison, thought generally to exist, is set aside, and that we are normally brought to the only agency available to account for the process: *i.e.*, the adrenals. But why does the chocolate methæmoglobinic blood not assume the arterial hue by exposure to air? Can we concede that whenever, in the organism, the hæmoglobin-molecule becomes dissociated, its constituents are all eliminated with the excretions? Evidently not. Even in chlorosis, in which hæmic respiration is greatly impaired, it is not, of course, abolished, and the components of the hæmoglobin-molecule must, in a measure, hold together, though loosely combined. But evidently some constituent capable of taking up oxygen must be missing in the methæmoglobinic blood referred to, to account for its inability, when exposed to the air, to become arterialized. Now, the adrenals being rendered insufficient by the drugs mentioned *plus* the known affinity of their secretion for oxygen, clearly suggest, it seems to us, that, if the methæmoglobinic blood could not be oxidized outside the body, it is because it lacked the suprarenal secretion. This tends to show that the suprarenal secre-

tion, which, as we now know, is constantly being supplied to the body, is oxidized in the course of the respiratory process.

In the light of all that has already been said concerning the effects of stimulation on the adrenals and the signs of insufficiency, the symptoms that follow amyl-nitrite inhalations, as described by Professor Wood, clearly depict the course of events. "The most prominent symptoms induced when amyl nitrite is inhaled by a man in moderate quantities," says this author, "are a sense of great fullness and distension of the head, amounting at last to severe pain and accompanied by intense flushing of the face." We can easily recognize here the result of a sudden spurt of suprarenal activity. The central vascular trunks and all the *muscular* vessels, veins, etc., are suddenly contracted, while the peripheral capillaries are dilated, giving rise to the cerebral pressure, the flushing, etc. That this dilation occurs independently of the spinal cord is sustained by the experiments of Wood and Lauder Brunton, which showed that its division did not prevent the peripheral congestion. "A deep, labored respiration, an exceedingly rapid and violent action of the heart," are next referred to, but the line where suprarenal insufficiency begins is not clearly defined—evidently, since, to use Wood's words, "the succession of these phenomena is usually so rapid that often they seem to be simultaneous."

Yet we have precisely at this point additional testimony that we must be dealing with suprarenal secretion, since Wood remarks: "But it is said that the cardiac disturbance is sometimes very distinctly manifest *before* the other symptoms." We have seen that the heart is the first organ reached by the secretion, and it must therefore be first to receive the brunt of the suprarenal principle. These facts are also sustained by the experiment of Bock on an isolated mammalian heart, which showed that nitrite of amyl has no effect upon the heart itself. The stage of suprarenal insufficiency is strikingly described: "After poisonous doses," continues Professor Wood, "the symptoms have been great pallor; usually dilation, but sometimes contraction, of the pupils; excessive muscular relaxation; slow, scarcely perceptible pulse; hæmoglobinuria, and irregular respiration." The morbid effects of suprarenal insufficiency—*i.e.*,

of dilation of the central vascular trunks, contraction of the peripheral capillaries, etc.—are self-evident.

That the adrenals are involved is further sustained by the observation of Lauder Brunton that if the descending aorta be tied high up no perceptible fall of pressure is produced by the amyl salt for some time. It is to be presumed that the ligation was practiced above the suprarenal vessels. "In lower animals," says Wood, "the first stage of the action is like that just described in man. After this the breathing becomes violently hurried and panting, progressive muscular weakness and diminution of reflex activity ensue, and finally death from failure of respiration. . . . A very peculiar symptom is that a long time before death both the arterial and the venous blood become of a nearly uniform chocolate color." The simultaneous occurrence of these phenomena clearly defines the morbid process. The chocolate-red blood, though still able to absorb oxygen, does so "very imperfectly"; hence the "violently hurried and panting" breathing to compensate by the number of respirations for the lessened oxidation. The general metabolism, impaired through imperfect hæmic respiration and therefore lessened oxidation, accounts for the rest: a symptom-complex with the suprarenal glands as starting-point.

In view of all these facts, the manner in which methæmoglobin is formed in the organism after poisoning seems to us to be as follows: *The adrenals supply an oxidizable principle to the blood. When a poison causes insufficiency of these glands, a compound inferior in its oxygen-absorbing power to hæmoglobin is formed, namely: methæmoglobin. The presence of this pigment in the blood is attended with more or less marked impairment of the respiratory function.*

HÆMATOPORPHYRIN.—How is this pigment formed in the organism as a result of poisoning? Sulphonal and trional have furnished, of all toxics, the greatest number of recorded cases of hæmatoporphyrinuria, and will therefore be used as the basis of this analysis.

Hæmatoporphyrin is stated by Garrod[75] to be present in normal urine in minimum quantity, in solid excreta, and

[75] Garrod: Lancet, Nov. 10, 1900.

meconium, while Stokvis[76] found it in bile and Taylor and Sailer[77] in blood collected post-mortem. As to its origin, Garrod refers to the observations of Keyser,[78] who found "that a change of diet from red meat to white meat without vegetables caused the disappearance of the normal trace from the urine, but that it returned when green vegetables were added to food." This is in accord with Stokvis's view, that a part of the urinary pigment is derived from the food and that even chlorophyl, from which a very similar pigment may be obtained, may contribute to its formation. Garrod does not believe, however, that the bulk of the urinary or fæcal hæmatoporphyrin has such an origin, though he found it associated with milk diet in one case, and states that it may be found in the fæces of sucklings. He is inclined to favor the view, therefore, that hæmatoporphyrin in excess is an indication of hæmolysis, and considers that "we are justified in concluding that the *hæmatoporphyrin of the body has hæmoglobin for its parent-substance.*" Still, when the question is put to the test "by examining the blood in cases in which unusual amounts of the pigment are being excreted and by examining the urine in cases in which active hæmolysis is known to be in progress," he finds them to "return the same answer: viz., that there is no necessary connection between excess of hæmatoporphyrin in the urine and excessive hæmolysis." In pernicious anæmia, "a disease in which hæmolysis is an essential feature, urinary hæmatoporphyrin is not increased *unless complicating conditions are present.*"[79]

This conclusion, when analyzed in connection with the data we have so far submitted concerning the relations between the suprarenal glands and hæmolysis, is fully sustained. Sulphonal, trional, and other toxics capable of giving rise to hæmatoporphyrinuria seem only to do so *when the suprarenal glands or their centers are more or less diseased,* the amount of pigment in the urine corresponding in a measure to the degree of insufficiency present. Disease of both adrenals may exist, as

[76] Stokvis: Zeitschrift für klin. Med., Bd. xxviii, p. 1, 1895.

[77] Taylor and Sailer: Contributions from the William Pepper Laboratory; quoted by Garrod, *loc. cit.*

[78] Keyser: Dissertation, Freiburg, 1897.

[79] The italics are our own.

we have seen, without interfering with the general physiological operations with which they are concerned until a very small proportion of normal tissue is left. A demand for suprarenal *protective activity* caused by the presence of a toxic in the blood taxes this physiologically adequate remnant more or less severely according to the dose and power of the toxic exhibited. If the stage of *total* suprarenal sufficiency, as the result of tuberculosis, syphilis, etc., is still remote, an agent, such as sulphonal, may be given for a long time before it causes a high degree of adrenal insufficiency to bring on *marked* hæmatoporphyrinuria; if, on the other hand, but a vestige of normal suprarenal tissue just sufficient to sustain life only remains, but a few doses are sufficient to cause it. Keith Campbell's case of hæmatoporphyrinuria, in which the most marked morbid change observed post-mortem was hyaline degeneration of both adrenals, may again be referred to in this connection. Only two 15-grain doses of sulphonal had been taken by the patient. The symptoms outlined by the following broken sentences: "Very poor circulation, blue œdema, coldness of the extremities . . . markedly-paretic flexors. . . . Breathing a constant struggle; Cheyne-Stokes breathing . . . pulse rapid and thready . . . patch of rusty staining over parietal region," etc., sufficiently indicate advanced suprarenal insufficiency to show a direct correspondence with the post-mortem findings.

To illustrate the effects of less advanced disease of the adrenals when sulphonal is used, the case recently reported by R. Waldo[80] may be cited. Here the drug had been taken during a prolonged period before the urine assumed the typical cherry-red or port-wine-like color. The rapid pulse (180), prostration culminating in general paresis, a "scarcely-moving diaphragm," and other symptoms also point here to disease of the adrenals. An interesting case of this kind, reported by Stuart Hart,[81] was attended with marked cardiac disturbance. That temporary reduction of a stimulus corresponding to that attributed to the suprarenal secretion was a factor in its production is suggested by the fact that "with the improvement

[80] R. Waldo: British Medical Journal, June 15, 1901.
[81] Stuart Hart: Amer. Jour. of the Med. Sciences, April, 1901.

in the *muscular tone*, the *dilation* and valvular incompetence entirely disappeared, leaving a normal heart."

It is only occasionally, and, in fact, very rarely, that hæmatoporphyrinuria is sufficiently marked to give the urine the cherry-red or even pinkish color observed in these cases. The coincidence of sufficiently advanced suprarenal insufficiency and the administration of the remedy is likewise rare, especially in presence of the fact—to be shown later on—that suprarenal disease is only traceable to conditions in which toxics of various kinds, including toxins, have given rise to serious general disease. When the adrenals or their center are normal, it is probable that only excessive or large doses of sulphonal or trional can produce a marked degree of hæmatoporphyrinuria. Kast and Weiss[82] produced it twenty-five times out of one hundred experiments in rabbits, but only by means of large doses. In dogs they could not bring it on, notwithstanding repeated and prolonged experiments.

If, as thought by Garrod, "the hæmatoporphyrin of the body has hæmoglobin for its parent-substance," how does it become dissociated from the latter? Chemically, they are, so to say, only two reactions apart: When hæmoglobin is treated with an acid or a strong alkali, hæmatin: *i.e.*, methæmoglobin, is formed; when the latter in turn is treated with sulphuric acid, it is deprived of its iron and becomes iron-free hæmatin: *i.e.*, hæmatoporphyrin. The general belief that the drug acts directly upon the blood is obviously untenable; indeed, it seems hardly reasonable to expect that a few 15-grain doses, administered twenty-four hours apart, will produce upon the seventeen pounds of blood in the organism effects which in the laboratory are only obtained with sulphuric acid or an equally active reagent. In fact, Kast and Weiss[83] were totally unable to obtain hæmatoporphyrin from extravasated blood by means of sulphonal, notwithstanding the use of several processes. With vulnerable organs, such as the diseased adrenals, to bear the brunt of the toxic process, on the contrary, a logical connection is established between the violent phenomena witnessed and the comparatively benign exciting cause. The many con-

[82] Kast and Weiss: Berliner klin. Wochenschrift, July 13, 1896.
[83] *Ibid.*

tradictory physiological effects observed with sulphonal as well as with other drugs in this connection, and the multiplicity of causative agents which may give rise to hæmatoporphyrinuria, are likewise accounted for. On the whole, it seems reasonable to conclude that, *while hæmatoporphyrinuria may be caused in normal subjects when excessive doses of the toxic agency enter the blood, it may be caused by small doses when the adrenals or their center are diseased, the intensity of the effects varying with the dose and the degree of insufficiency the adrenals have reached.*

In support of this view we have, in a proportion of cases, besides the symptoms of suprarenal insufficiency, a more or less marked reduction of hæmoglobin. F. Müller[84] reported a case in which the hæmoglobin ratio fell to 45 per cent. during the most active stage of hæmatoporphyrinuria and gradually returned to 85 per cent. as the urine became gradually cleared of its pigment. The parallelism between the percentage of hæmoglobin and the variations in the urine is well illustrated in a case reported by J. Calvert,[85] probably suffering from tuberculous adrenals, with an acute exacerbation of suprarenal insufficiency of unknown origin, no sulphonal or trional having been taken by the patient. The hæmoglobin percentage was at first 48 per cent. and the red corpuscles 2,292,000. Gradually the hæmoglobin reached 62 per cent. and the red corpuscles 3,968,000, these changes covering a period of six days. "After this," says the author, "the percentage of hæmoglobin and the number of the red corpuscles steadily increased and the urine gradually returned to its normal color."

This should not be taken to mean, however, that in all cases of hæmatoporphyrinuria the ratios of hæmoglobin and of red corpuscles keep pace with the alterations witnessed in the color of the urine. In Keith Campbell's admirably reported case the blood-count showed throughout 7,000,000 red corpuscles, and, when breathing had become "a constant struggle" and convulsions had occurred, the ratio became even greater: *i.e.*, "rather over 7,000,000." Yet in this case it was not the

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[84] F. Müller: Wiener klin. Wochenschrift, p. 252, 1894.
[85] J. Calvert: Lancet, Dec. 22, 1900.

parallelism between the hæmatoporphyrinuria and the hæmoglobin that had ceased, it was that with the red corpuscles, since "the percentage of hæmoglobin" as taken by Dr. Oswald in this case "was 49 per cent." Thus, while this ratio was very low, the blood-corpuscle ratio was exceedingly high: a fact easily accounted for by the persistent vomiting which represents one of the striking features of the case, and doubtless due to *effusion of blood-serum into the stomach through the evident engorgement of central vascular trunks.* The loss of fluids simply condensed the blood; hence the high corpuscular ratio. But for the vomiting the blood-examinations would probably have given results very similar to those of the other cases mentioned. In truth, the blood-count furnishes but little, if any, reliable information in any case of hæmatoporphyrinuria, unless the ingestion and loss of fluids by the gastro-intestinal and urinary tracts and the skin be accurately established, supported by a specific-gravity ratio of blood taken from a large vessel. The same cannot be said of the hæmoglobin ratio, which seldom exceeds 70 per cent. while the cherry-red urine is present, and often reaches below 50 per cent.

Are we dealing with a stage in the dissociation of hæmoglobin, or with a reaction in which only a portion of the blood is involved? To consider, as previously implied, the formation of hæmatoporphyrin as a stage in the hæmolytic process would implicate an antecedent reaction: *i.e.*, that affording methæmoglobin as end-product. But in none of the reported cases which have come to our notice so far is the chocolate-colored urine said to have preceded the port-wine-red urine. When the latter fades off, it does not assume the typical color of methæmoglobinuria, but becomes dark claret, then light claret, pinkish in hue, etc. In other words, it presents a totally different aspect, and it is evident that it does not characterize a stage of blood-disintegration of which the following are the steps: Hæmatoporphyrin + iron = methæmoglobin; methæmoglobin + proteids = hæmoglobin. Again, hæmatoporphyrin being iron-free hæmatin, we cannot, as was the case with methæmoglobin, grant it the power to take up the oxygen with which life is maintained. Side by side with the impaired blood-elements there must exist approximately-perfect blood. The only

logical conclusion available, therefore, is that only a portion of the blood is directly involved. We can thus account for the cases of hæmatoporphyrinuria in which apparently normal health is present—though the reserve of suprarenal tissue is steadily being destroyed by some morbid process—and brought on by an intercurrent disorder in which a toxic action prevails: sulphonal, trional, lead, rheumatism, gout, etc., and particularly hepatic disorders, in which cloudy swelling and fatty degeneration are so prominent.

What is the nature of the process? Kast and Weiss,[86] in their study of the hæmolytic effects of sulphonal upon the blood, state that under certain pathological conditions, and especially in anæmic women, "there exists a loose combination of the blood-pigment." The same remark is applicable with insufficiency of the suprarenal glands as the underlying factor of the hæmolytic process, on the condition, however, that the suprarenal glands be recognized as producing a secretion endowed with the marked affinity for oxygen which it is now known to possess, and that this affinity be considered a part of the process. It is clear that deficiency of suprarenal secretion must carry with it "a loose combination of the blood-pigment," since oxidation, as shown by the character of the reducing agents required to disintegrate blood *in vitro*, represents the principal bond of union between all the main bodies involved. With both organs diseased, such a condition of the blood is always more or less marked, and, when an acute toxic intercurrent process suddenly appears, this "loose combination" becomes accentuated in proportion to the intensity of the morbid effects upon the glands. If these effects are overwhelming, the "blood is everywhere scarlet," to use Rabuteau's expression in reference to his oxalic-acid cases; if they are not, the clinical picture presented is that of the cases reported, in which the original disease shows more or less marked tendency to pervert the characteristic suprarenal symptoms that appear when only one pathogenic factor is present. Here, however, an additional source of blood-disintegration appears on the field.

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[86] Kast and Weiss: Berliner klin. Wochenschrift, July 13, 1896.

As already stated, acids disintegrate hæmoglobin, hæmatin being formed. This only occurs, however, in the *presence* of oxygen. In the lungs, therefore, the "loose combination" involving imperfect absorption of oxygen, while defective respiration is further encouraged by the imperfect or arrested action of the respiratory muscles, the process of hæmoglobin disintegration, if at all influenced, is rather interfered with than encouraged. It is consequently not in the respiratory area that the process occurs, and, if elsewhere in the organism, the reaction must be one in which oxygen is absent. We have already seen, when chlorosis was studied, that, when hæmoglobin is treated with an acid in the *absence* of oxygen, a hæmochromogen first appears which slowly loses its iron, the end-product being hæmatoporphyrin. What was then said, therefore, is also appropriate in connection with the process through which hæmatoporphyrin is formed: *i.e., the tissues play the part of the acid employed in the laboratory to disintegrate hæmoglobin: they abstract its oxygen. The imperfect condition of the blood involving reduced oxidation, oxyhæmoglobin is not always formed, and arterial blood fresh from the lungs, while still containing enough of this compound to more or less perfectly carry on the vital processes, also contains a more or less great proportion of free hæmoglobin. Under these conditions, the avidity of the tissues for oxygen causes them not only to absorb the one molecule of this gas from the oxyhæmoglobin, but also to make up for the deficiency by taking up oxygen from hæmoglobin: i.e., the only remaining source of supply. We thus have in the blood the precise conditions required for the reaction outlined, namely: absence of oxygen and a powerful reducing agent,—the tissues,—and, therefore, obtain as end-results free iron and hæmatoporphyrin.*

This suggests another query. The microscopical examinations of adrenals taken at random at autopsies have shown Arnaud that 36 per cent. of all adrenals contain evidences, more or less marked, of fatty degeneration. Why, under these circumstances does hæmatoporphyrinuria, which may be induced by a large number of toxic disorders, not appear more frequently? The answer is readily available: *hæmatoporphyrin, bilirubin, iron-free hæmatin, and hæmatoïdin are isomers: i.e.,* the same body is now recognized under different names.

Important in this connection is the close relationship between hæmatoporphyrin and urobilin, formed when the former is subjected to putrefactive conditions or nascent hydrogen, which is present in very small amount in normal urine. This pigment also occurs in fæcal matter, and is here recognized as "stercobilin." In both urine and fæces, however, it appears in excess, though apparently with no degree of parallelism, in many morbid conditions. In acute fevers, for instance, it may be increased to five or six times its normal ratio; especially is this the case in pneumonia, typhoid fever, and the septic fevers, in which rapid disintegration of the blood-elements occurs. "In febrile disorders of almost every kind," says Garrod, "temporary urobilinuria may be met with, the duration of which usually corresponds with that of the pyrexia. In diseases of the liver, the urobilinuria is usually persistent, as is well seen in cases of cirrhosis, malignant disease, or passive congestion secondary to cardiac or pulmonary troubles. . . . In diseases attended by excessive hæmolysis, and during the absorption of extravasated blood, there is apt to be conspicuous urobilinuria, and, unless complications are present, there is no corresponding increase of uroerythrin or hæmatoporphyrin. Such urines have a warm orange color, which is readily recognized by a trained eye, and at the apex of a conical glass a pinkish tinge is usually seen." He refers to the valuable diagnostic signs persistent urobilinuria affords in pernicious anæmia, as shown by Mott and Hunter, and to his personal observation that there is likewise a marked excess of urobilin in the fæces. It follows *hæmorrhages* and especially *intracranial hæmorrhage*, hæmorrhagic infarctions, pelvic hæmatoceles, etc.

The "chief seat of formation of urobilin is undoubtedly the intestinal canal. This can only be gainsaid," says Garrod, "by denying the identity of the urinary and fæcal pigments." (The identity of these is evident, and he refers to combustion experiments conducted personally and with F. G. Hopkins, in which this is confirmed.) Several investigators consider the bile as the only source of urobilin. "There is strong evidence," says Garrod, "that the urobilin in the bile itself is of intestinal origin," while "it is equally clear that the substance from which the intestinal urobilin is formed is the bile-pigment."

A logical conclusion suggests itself in the presence of these facts: *i.e., that the changes undergone in the liver are a part of a cycle with the intestine as a starting-point.* And so it must be, since, again using Garrod's words, "it seems to be clearly established that absorption from the intestine does take place, and that, of the urobilin so absorbed, some is *excreted with the bile* and some with the urine."

Bilirubin, from which at least a portion of the urobilin found in the urine and fæces is derived, is not found in either of these excreta. It disappears on its way down the intestine and is replaced by large quantities of urobilin. When, however, bilirubin does, under certain morbid conditions, escape with the fæces, urobilin does not appear in the latter. How does this transformation in the intestine occur? Garrod states that the radical change involved is attended with the elimination of nitrogen, and that there is much evidence to show that it is brought about by bacteria. Bile inoculated with fæcal matter and placed in an incubator, for example, yields urobilin rapidly, while the bilirubin simultaneously disappears. F. Müller, A. Schmidt, and Esser also "obtained urobilin by cultivating intestinal bacteria in broth to which an alkaline solution had been added." The same results were obtained by Garrod and Drysdale, but only when oxygen was present. While the absolute identity between this and the natural pigment has not as yet been established, the artificially produced urobilin was found to possess the chief properties of the latter.

In the body the change chiefly occurs in the *upper part of the large intestine,* the contents of which are alkaline, while those of the small intestine are acid. This is a feature of considerable importance evidently, since Esser found that "acidity of the culture-medium inhibited the change which took place under the influence of bacteria in alkaline broth." Garrod further states that the green stools occasionally seen in typhoid fever are always distinctly acid in reaction, and are urobilin-free, the urobilin also disappearing from the urine. When alkalinity recurs, urobilin likewise reappears. Yet, the intestinal area in which the urobilin is formed from bilirubin varies greatly in different individuals, sometimes extending to the jejunum; but experiments by Vaughan Harley suggest that the

process of transformation is most active when bacterial processes are likewise so.

An anomalous phase of the process, however, is the fact that "the quantity normally present in the fæces is far larger than that which enters the intestine with the bile," while, as shown by F. Müller, "complete occlusion of the common bile-duct causes urobilin to disappear from the fæces, and a few days later from the urine also." Garrod states that the latter observation has been repeatedly confirmed. Yet, in animals with biliary fistula, while no bile enters the intestine, the urine still contains urobilin. In Copeman and Winston's[87] case of biliary fistula, in which no bile had entered the intestine, the fæces were uncolored by stercobilin; nevertheless the urine still contained urobilin. But, even leaving urobilinuria out of the question, it is difficult to understand how occlusion of the bile-duct can govern a quantity of pigment greater than that which the liver takes up: *i.e.*, how it can affect pigment which the liver has not received. This is but one instance of several available. Garrod, alluding to the general conclusions suggested by the data presented in his excellent paper, says: "When, however, we apply this theory to clinical facts, difficulties are encountered which cannot as yet be wholly met, and it soon becomes evident that the theory, as above stated, is inadequate, and that some amplification or modification of it is necessary." This amplification seems less remote when the physiological functions of the suprarenal glands are introduced as factors in the process involved.

The fact that urobilinuria is marked in diseases such as rheumatism, cirrhosis of the liver, etc., in which hæmatoporphyrinuria is also observed, suggests a common origin. Garrod refers to urobilin and its chromogen "as widely distributed in the human body. . . . They have been found in the bile removed from the gall-bladder during life, as well as in that obtained post-mortem, and are met with in the blood and in serous effusions. . . . As obtained from all the above sources, specimens of urobilin agree in all their properties and are clearly identical in their nature." As to the origin of uro-

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[87] C. W. Purdy: "Uranalysis and Urinary Diagnosis," p. 46, fifth edition, 1900.

bilin, the author, after reviewing the main hypotheses bearing upon this point, says: "It will be seen that the above theories, one and all, start with the assumption that *urobilin is derived from hæmoglobin, either directly or through the intermediate stage of bile-pigment*," and refers to Thudicum as alone maintaining that urobilin is a product of decomposition of urochrome: a view which need not represent an exception, since this pigment can likewise be traced back to hæmoglobin.

"The very small amount present in normal urine and its complete absence from that of certain animals, such as dogs, in whose intestines it is present in considerable quantity," says Garrod, "suggest that the pigment is, in part, subjected to change in its passage through the body, and is excreted in some altered form." This is quoted merely to emphasize the fact that the formation of any of the pigments referred to, even stercobilin, is not followed by its immediate evacuation from the organism, but that the transformation from bilirubin to urobilin-stercobilin on the colon side of the ileo-cæcal valve probably represents but the first step of various transformations of a biochemical nature in which the tissues at large take part, but of which certain organs are the primary seat. Urobilin, as shown by Riva, when introduced into an isolated loop of intestine undergoes absorption. This and other evidence available distinctly indicates that this pigment enters the circulation.

We will assume, as a working hypothesis, that urobilin, far from always representing a product of waste,—some of it at least,—is constantly traversing the organism, fulfilling its various missions and returning to the ileo-cæcal neighborhood via the liver. It will then become apparent that the statement—"Its disappearance from the urine when the bile is occluded . . . disposes of the theory that urobilin is formed from bilirubin in the tissues at large, for, under such circumstances, *although the tissues remain loaded with bilirubin*,[88] the excretion of urobilin is arrested"—from Garrod's pen seems to lose weight. If the above hypothesis obtains, complete occlusion of the common bile-duct, as carried out by Friedrich

[88] The italics are our own.

Müller, can do but one thing: *i.e.*, block the normal functional cycle. Urobilin will of necessity disappear from the fæces and from the urine, since the functions of the organism will continue; and, retransformed into bilirubin, the pigment, in its turn, must accumulate in the organism behind the obstruction. It is for this reason, therefore, that "*the tissues remain loaded with bilirubin.*" The close relation between hæmatoporphyrin and bilirubin further affirms itself when we compare their formulæ:—

$C_{32}H_{32}N_4O_5$ — Hæmatoporphyrin.

$C_{32}H_{36}N_4O_6$ — Bilirubin.

When we consider that the latter differs only from the former by a surplus of oxygen and hydrogen ($C_{32}H_{32}N_4O_5 + 2H_2O - O = C_{32}H_{36}N_4O_6$), we are reminded of the avidity of the tissues for oxygen, referred to when the blood-changes leading to hæmatoporphyrinuria were analyzed. We then noted that the tissues, in the *absence* of oxygen, took the place of the laboratory acid which removed oxygen from hæmoglobin, leaving a chromogen which slowly lost its iron, and which, minus its iron, became iron-free hæmatin, or hæmatoporphyrin. But we must remember, in this connection, that the reaction given as illustration refers to a laboratory operation and to sulphuric acid or an equally powerful reagent, and that *in the tissues the avidity for oxygen continues when blood-disintegration has reduced respiratory oxidation to a minimum just compatible with the continuation of life, and they continue, nevertheless, their deoxidizing effect,* more and more depleting the blood of its O. *In the majority of diseases attended with blood-disintegration we do not meet with hæmatoporphyrinuria, therefore, but with urobilin in the urine and stercobilin in the fæces,* both being formed when the first named or its isomer, bilirubin, are exposed to putrefactive processes, etc.; so that we do witness hæmatoporphyrinuria, though slightly modified, with great frequency. The suprarenal insufficiency involved also reduces the normal formation of oxyhæmoglobin, but to a less marked degree, probably because the disease is not complicated with adrenals previously weakened by advanced disease, and the avidity of the tissues is correspondingly less. Instead, there-

fore, of obtaining hæmatoporphyrin as end-result, we obtain *hydrobilirubin*, the reaction being approximately as follows:—

$$2(C_{32}H_{36}N_4O_6) - O_2 + 4H_2O = 2(C_{32}H_{36}N_4O_5.2H_2O)$$

Bilirubin. Hydrobilirubin.

Hydrobilirubin, as is well known, is usually termed "*febrile urobilin*," though it often appears in diseases in which fever does not occur.

All these facts suggest another conclusion: *i.e.*, that *hæmatoporphyrin, bilirubin, hæmatoïdin, and its other isomers, as hæmoglobin derivatives, are restored to the pulmonary circulation by reabsorption from the intestine, and again used in the building up of hæmoglobin.* This is sustained by what evidence is available. It also satisfies the requirements of all the experiments referred to in Garrod's paper, which the other hypotheses outlined therein failed to meet.

The reduction to a single pigment of all the isomers of hæmatoporphyrin is not only important from the clinical standpoint, but it will assist us in elucidating various features of the question in point: *i.e.*, the relationship between the adrenals and the respiratory function. Especially does this apply to hæmatoïdin, one of the pigments referred to. "In old blood-clots in the body," says Professor Foster, "the hæmoglobin of the clot becomes in time transformed into an iron-free body which has been called hæmatoïdin, but which, both in composition and reactions, appears to be identical with bilirubin." Again, he refers to the identity of both compounds in the following words: "Virchow[89] has described the gradual changes in old blood-clots, such as those of cerebral hæmorrhage, which lead to the presence of the so-called hæmatoïdin-crystals. Though these have not been obtained in sufficient quantities to enable their composition to be finally fixed by a chemical analysis, still, the identity of their crystalline form with that of bilirubin, and the fact that they both give the same play of colors when oxidized, as in Gmelin's test, justify the assumption that *hæmatoïdin and bilirubin are identical.*"[90]

The presence of hæmatoïdin in conditions of advanced

[89] Virchow: Archiv für path. Anat., Bd. i, S. 383.

[90] The italics are our own.

blood-disintegration and its connection with suprarenal insufficiency have been fully emphasized, but an observation of Boinet's—already referred to—will prove interesting in this connection. Referring to the blood of one of the rats which survived removal of both adrenals several months, and in which bronzing had occurred, this author[91] says: "*The venous and arterial blood contained a large proportion of black pigment, with crystals of hæmatoïdin.*" The same black pigment, we have seen, was also found by him in more or less great quantities in 75 per cent. of 109 decapsulated rats; was traced everywhere in the body, and was found *similar* to that obtained from the *bronzed spots* of two fatal cases of Addison's disease. But this did not only occur in decapsulated animals, but likewise in a series in which lesions had been caused in the adrenals by means of chemical and bacterial agencies.

Why should removal of the suprarenal glands be followed by the accumulation of hæmatoïdin in the tissues? Hæmatoïdin-bilirubin being a derivative of hæmoglobin, we are again, and from another direction, led to the conclusion that the suprarenal glands supply a secretion which serves to hold in combination the various constituents of hæmoglobin.

THE SECRETION OF THE ADRENALS AND THE RESPIRATORY PROCESS.

That the secretion of the adrenals can endow the hæmoglobin-molecule with its power to take up oxygen seems to us beyond question. Indeed, removal of the adrenals of a normal animal does not remove the various constituents of hæmoglobin from its organism. The iron to which the affinity of the blood-pigment for oxygen is now ascribed, and all of the other elements whose chemical affinity is supposed to suffice for the holding together of the hæmoglobin-molecule, are present. The surroundings of all these constituents are not changed; corpuscles, plasma, temperature are present. Why, therefore, do they not, in virtue of their affinity, hold together? When the suprarenal glands are removed we not only have an accumulation of hæmatoïdin and other pigments in the blood, but

[91] Boinet: Marseille Médical, April 15, 1896.

there occur phenomena which simultaneously point to the cessation of suprarenal functions and to defective oxidation of the tissues. With dyspnœa appears muscular weakness: the muscles of the thorax, the diaphragm, have lost their tone—their *pabulum vitæ*, as it were. But this does not only indicate the loss of tone which the suprarenal secretion imparts; there is gradual loss of power, ending in paralysis. Why should this occur if metabolism can still continue? Nothing has been changed in the organism but organs which are only supposed to give *tone* to the muscular elements. And still metabolism is obviously arrested. That it is due to the absence of oxygen and arrest of oxidation—*i.e.*, combustion within the tissues—is proven by the fact that *the temperature is lowered everywhere.* In all of the rats in which Boinet took the rectal temperature marked hypothermia was noted. The opposite conditions of temperature between the central organs and the peripheral tissues no longer obtain here; it constitutes a function of which the suprarenal glands are the center and which gradually ceases when these are removed.

Gourfein[92] has experimentally shown that the destruction of these organs greatly influenced nutrition. One-twentieth of both capsules sufficed to keep animals alive from 18 days to 9 weeks; but, notwithstanding the fact that they took their normal food, there was steady loss of weight, death occurring when the half of their normal weight had been lost. That this cannot be ascribed to trophic lesions of purely nervous origin is shown by the fact that motor nerves and even their intramuscular ramifications were found to have lost none of their electrical excitability.

Evidently metabolism ceases when the suprarenal glands are removed, while the other features referred to point to arrest of oxidation in the tissues as the cause of this cessation. This, in addition to the fact stated, that the constituents of hæmoglobin lose their affinity for one another when these organs are removed, and the invariable presence of suprarenal symptoms when toxic elements are sufficiently active to cause methæmoglobinuria, hæmatoporphyrinuria, etc., or other evi-

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[92] Gourfein: Revue inter. de Thérap. et de Pharm., May 17, 1896.

dences of blood-dissociation, warrant the conclusion, it seems to us, that:—

The adrenals supply a secretion which serves to hold in combination the various constituents of hæmoglobin and which simultaneously endows the hæmoglobin-molecule with its power to take up oxygen.

As in man the pulmonary tract alone is the seat of the respiratory process, we are again brought to the lungs as the organs to which the suprarenal secretion is distributed. If we now recall (1) the marked respiratory disorders which attend not only the extirpation of the adrenals, but also advanced disease of these organs; (2) that the pulmonary tissues do not respond to the action of suprarenal extract as do other tissues, even warm extract failing to prove active as elsewhere; (3) that the adrenals produce a secretion which could be traced no farther than the lungs, the assumption that so close a physiological relationship between these organs and the suprarenal glands exists seems to stand on a sound foundation.

We have already referred to the fact that the presence of hæmatoïdin, a derivative of hæmoglobin, in the tissues after removal of both adrenals suggests, as a working hypothesis, that the secretion of these organs serves to keep united the various constituents which enter into the formation of hæmoglobin, and that it is concerned with the affinity of this compound for oxygen. Mathias Duval was shown to have referred to the vulnerable points of the present conception of the respiratory chemico-physiological process, and the need of "an action having for its object to rapidly dislodge the carbonic acid," mere gaseous diffusion failing to satisfy the demands of various phases of this process. While adducing reasons for the assumption "that the combination of oxygen with the blood-corpuscles (oxyhæmoglobulin) plays a rôle analogous to that of an acid," Professor Duval is also stated to have recalled Robin and Verdeil's view in respect to the existence of a hypothetic "pneumonic acid," and also Garnier's ultramarine-blue test, which suggested that "a strong acid must exist in the lungs," though "chemical analysis has not disclosed a specific acid" in these organs.

But these are not the only investigators who have felt the

weakness of prevailing views as regards the intimate processes of pulmonary respiration. Reichert,[93] referring to the interchange of O and CO_2 between the alveoli and the blood, remarks, after reviewing the generally accepted doctrines: "It is, however, impossible, under certain conditions, and possibly under ordinary conditions, to account for the transmission of all of either the O or the CO_2 by the laws of diffusion. Bohr[94] found, in experiments upon dogs, that the tension of oxygen in arterial blood is almost invariably higher than the partial pressure of oxygen in the lungs, and in some instances considerably higher. His records of CO_2, while lacking uniformity, are of like import, and indicate that the tension of CO_2 in the blood is lower than the partial pressure of this gas in the lungs. Although Bohr's results have met with much adverse criticism, they have received substantial support in the recent researches of Haldane and Smith[95] on mice, birds, dogs, and other animals. They found that the normal oxygen-tension in arterial blood is always higher than in alveolar air, and they were consequently led to conclude that the transmission of O between the alveoli and the blood cannot be satisfactorily explained by mere diffusion. Moreover, about twice as much argon exists in solution in the blood-plasma as can be accounted for by physical laws. Facts of this kind are explicable on the hypothesis that the living tissues are, as contended by Ludwig, Bohr, and others, actively engaged in the process, but our knowledge is as yet too incomplete and contradictory to justify its acceptance." "In Bohr's experiments," says G. N. Stewart,[96] "in some of which the animals were made to breathe air containing carbon dioxide in various proportions, the tension of that gas in the air of the lungs varied from 5.8 to 34.6 millimeters of mercury, while in arterial blood, taken at the same time, it usually ranged from 10 to 38 millimeters, and was often less than in the alveolar air. If we accept these results we seem shut up to the conclusion that carbon dioxide does not pass through the walls of the alveoli by diffusion.

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[93] Reichert: "American Text-book of Physiology," vol. i, 1900.
[94] Bohr: Skandinavisches Archiv für Physiologie, Bd. ii, S. 236, 1891.
[95] Haldane and Smith: Journal of Physiology, vol. xxii, p. 231, 1897.
[96] G. N. Stewart: "Manual of Physiology," p. 242, fourth edition, 1900.

And, although Bohr's experiments have been severely criticised, it does not seem improbable in itself that the physical process of diffusion is aided by some other process which may provisionally be termed secretion." "As to the oxygen, we are in the same position. Its partial pressure does not appear to be always higher, even under normal conditions, in the alveoli than in the arterial blood as it leaves the lungs. Indeed, Bohr found that, in the majority of his observations on dogs, the oxygen-tension was distinctly greater in the blood than in the pulmonary air. And Haldane and Smith, using a new method, have obtained a value for the oxygen-tension in human blood (26.2 per cent. equal to 200 millimeters of mercury) that even exceeds the partial pressure of oxygen in the external air and is about twice as great as that of the air of the alveoli. . . . Additional evidence in favor of the view that there is, besides diffusion, an element of selective secretion in the interchange of gases through the pulmonary membrane is afforded by a study of the gases of the swim-bladder of fishes."

Besides all the data recorded in this chapter, *generally recognized facts—i.e.*, facts generally known before this work was written—when submitted to a process of logical reasoning, also lead to the conclusion that an intimate relationship exists between the respiratory function and the suprarenal glands. That a physiological relation between these organs and the blood exists, is shown by the fact that, while characteristic "bronzing" pigment is a derivative of hæmoglobin, Addison's disease is known to be due to disease of the suprarenal glands. A "derivative" implicates the element of subdivision. Since, therefore, the "bronze" pigment is a derivative, the suprarenal glands must be concerned with the dissociation of the blood-pigment from which the "bronze pigment" is derived. This we know to be hæmoglobin; the suprarenal glands must, therefore, be connected with the dissociation of hæmoglobin. Again, since it is a lesion of the suprarenal glands that underlies this process, the glands must serve to keep the constituents of hæmoglobin together. To chemically disintegrate hæmoglobin we use reducing agents which act mainly by deoxidizing this body. Hence, the suprarenal glands must furnish a substance which supplies oxygen to the hæmoglobin constituents.

But, as we know that the suprarenal secretion, on the contrary, possesses a strong affinity for oxygen, it must hold the hæmoglobin constituents together through the effects of this property. The lungs are the only organs in man in which the blood becomes oxidized. Hence, the suprarenal secretion must also meet the hæmoglobin constituents in the lung, and, as its affinity for oxygen can only serve its purpose in the presence of this gas, the alveoli must be the seat of the process through which the hæmoglobin constituents are united with the suprarenal secretion. As the reagents used to chemically disintegrate hæmoglobin include acids which act mainly through their affinity for oxygen, any combination presenting a similar affinity for oxygen can chemically simulate an acid. *Hence, hæmoglobin, through its union with suprarenal secretion, acquires a degree of affinity for oxygen commensurate with that of the suprarenal secretion, and thus becomes sufficiently active as a reagent to simulate an acid.*

This deduction coincidently meets the needs of the respiratory process defined by Mathias Duval: A degree of affinity far higher than that thought to depend solely upon the mutual attraction shown by the various constituents of hæmoglobin is provided. As the hydrogen in hæmoglobin or the various constituents referred to seem at no time to be displaced by a metal during its peregrinations through the normal or diseased organism, the blood-pigment cannot be considered as an acid, and Robin and Verdeil's search for a "pneumonic acid" in the lungs was obviously fruitless. Yet, when it comes to Garnier's ultramarine-blue test, the powerful affinity conferred on the hæmoglobin by the suprarenal secretion fully accounts for the loss of color noted in the fluid injected in the lungs of guinea-pigs. Its contact with alveolar surfaces really meant contact with a powerful reagent capable of *simulating* "a strong acid" in its effects, though no acid, as chemistry interprets this term, could be said to be present.

Suprarenal insufficiency caused by the entrance of poisonous elements into the circulation gives rise, we have seen, to a condition of the hæmoglobin in which it is said to be "in loose combination." Evidently, then, the suprarenal secretion serves to hold the constituents of the blood-pigment together,

and since these constituents tend to fall apart when the secretion fails them, its flow into the circulation must be continuous. Again, we know that venous blood contains not only reduced hæmoglobin, but a considerable proportion of oxyhæmoglobin. The red corpuscles must therefore always be supplied with more oxygen than the tissues utilize: a fact which warrants the conclusion that even reduced hæmoglobin, under normal conditions, is always sufficiently supplied with this gas to preserve its integrity as a unit. But this conclusion in itself testifies to *the presence in the hæmoglobin-molecule of suprarenal secretion,* and therefore to the fact that, *as long as its integrity is preserved, it is capable of taking up an equivalent of oxygen in the lungs.*

This does not modify, however, the present teachings of physiology as regards the rôle of the blood-pigment in the circulation. "Undergoing no intrinsic change in itself," writes Foster, "the hæmoglobin combines in the lungs with the oxygen which it carries to the tissues; these, more greedy of oxygen than itself, rob it of its charge, and the reduced hæmoglobin hurries back to the lungs in the venous blood for another portion."

That gaseous diffusion and endosmosis are unimportant factors of the respiratory process seems probable in view of the foregoing facts. "Whenever oxygen is mixed with venous blood, even *in vitro* during experiments, the carbonic acid is immediately given off" writes Mathias Duval. "One is led to admit, therefore, that the combination of oxygen with the blood-corpuscle (oxyhæmoglobin) plays a rôle analogous to that of an acid and involving the elimination of carbonic acid from venous blood." The potent agency underlying the affinity of the blood-pigment for oxygen, we have seen, *simulates* an acid in its effects. The elimination of carbonic acid, therefore, includes the *physical* expulsion of a gas for which the hæmoglobin itself, when normally supplied with the suprarenal secretion, has less affinity than it has for oxygen. In carbonic-acid poisoning suprarenal insufficiency prevails, as it does in the case of poisons and venoms reviewed in this connection. Blood studied outside the body is, therefore, but an approximate and variable criterion of the physiological func-

tions themselves. Both in extravasated blood and in blood taken from a case of carbonic-acid poisoning the hæmoglobin must be in more or less loose combination: *i.e.*, more or less deprived of its complement of suprarenal secretion. The fact that so marked an affinity as that witnessed in *venous* blood in the experiment referred to still exists shows how active must be that exhibited by the blood of the organism when possessed of its full physiological attributes.

When we come to Bohr's experimental findings, which tend to show that "carbon dioxide does not pass through the walls of the alveoli by diffusion," they simply sustain what the presence of an agency capable of endowing the blood with a powerful affinity for oxygen at the seat of respiratory interchanges,—the walls of the alveoli,—would suggest, namely: the conclusion that *gaseous diffusion and endosmosis are unimportant factors in the pulmonary respiratory process, if they take any part whatever in the phenomena of which it consists.*

Bohr's statement that the pressure of the oxygen in the alveoli did not always appear higher, even under normal conditions, than in the arterial blood, and that in dogs he had found the oxygen-tension in the blood distinctly higher in the majority of his experiments than in the pulmonary air, and Haldane and Smith's observation, that in the human blood the oxygen-tension was about twice as great as that of the alveolar air, are likewise sustained. The hæmoglobin, owing to its powerful affinity for oxygen, takes it up from its surroundings regardless of the variations of pressure, and, unless the oxygen is proportionately replaced, it will entirely (Müller) exhaust the element containing it. *The relative tension of oxygen in the blood and in the alveolar air is not, therefore, a ruling factor in the process of physiological respiration;* and the higher oxygen-tension in the blood referred to, though subject to constant perturbations, physiological and pathological, seems but a normal consequence of the presence in that blood of so potent an agency for the absorption of oxygen as that represented by the suprarenal secretion.

If the views outlined in this chapter are based on solid premises, the process of *pulmonary respiration* is approximately as follows:—

1. The adrenals secrete a chromogen—a colloid, hyaline fluid —which leaves the organs through the suprarenal veins, and is mixed with the plasma of the venous blood in the inferior vena cava.

2. When the venous blood reaches the pulmonary alveoli, the marked affinity of the adrenalized plasma for oxygen causes it to absorb this gas from the alveolar air.

3. The carbonic dioxide in the blood is thus forcibly replaced by oxygen, and expelled with corresponding vigor.

4. The red corpuscles, after this operation, bathe in an oxygen-laden medium, and their hæmoglobin becomes reconverted into oxy-hæmoglobin.

The mechanism of respiration, and the manner in which the adrenal secretion and the air are brought into contact in the alveolar elements will be studied in a subsequent chapter.

As regards the relations between this process and the *preservation or dissociation of hæmoglobin*, the following deductions seem warranted:—

1. The periodical exposure of the hæmoglobin-molecule to the oxygen-laden adrenal secretion in the lungs serves to keep its constituents associated.

2. Deficiency, quantitative or qualitative, of adrenal secretion by reducing the oxygen-absorbing power of the plasma correspondingly reduces the mutual affinity of the hæmoglobin constituents.

3. When the molecular combination of the hæmoglobin constituents becomes sufficiently loose from this cause, portions of the hæmoglobin are detached and follow the arterial blood-stream in their reduced state, and the efficiency of the blood is reduced in proportion.

4. The physiological absorption of oxygen by the tissues not only reduces the oxyhæmoglobin, but further dissociates this adventitious hæmoglobin into its component bodies.

5. The component bodies of hæmoglobin thus dissociated are:

(a) Methæmoglobin or its isomer, hæmatin ($C_{32}H_{34}FeN_4O_6$).

(b) Hæmatoporphyrin or its isomers, iron-free hæmatin, hæmatoïdin, and bilirubin ($C_{32}H_{36}N_4O_6$).

(c) Hæmatoporphyrin (usually termed hæmatoïdin) appears in the blood when the adrenals are removed or when their functions

are totally inhibited by toxics; it is therefore the lowest of the cleavage products of the hæmoglobin-molecule.

(d) Hæmoglobinuria, methæmoglobinuria, and hæmatoporphyrinuria indicate, therefore, successive stages of adrenal insufficiency.

CHAPTER III.

THE INTERNAL SECRETION OF THE ADRENALS IN ITS RELATIONS TO THE GENERAL OXIDATION PROCESSES.

THE ADRENAL SECRETION AND THE OXIDIZING SUBSTANCE OF THE BLOOD.

Stimulation of the adrenals by means of a drug or toxic gives rise, we have seen, to a marked increase of functional activity in all organs. Quinine, for instance, causes wakefulness, congestive headache, and sometimes maniacal delirium, flushed face, spontaneous epistaxis, muscular twitchings resembling those caused by strychnine, active uterine contractions, etc. How explain this increased activity produced through these organs? It is evident that it must be due to the increased production of suprarenal secretion induced by the drug and a correspondingly enhanced activity of the oxidation processes. But how does the blood become surcharged with oxygen in order to produce these effects? Whether these be brought on by stimulation of the cerebro-spinal centers, increased blood-pressure, contraction of the central vascular trunks, or any other process, we are always brought back to the primary active factor: oxygen. Does the corpuscular hæmoglobin take it up in excess? This is hardly probable; since the hæmoglobin-molecule, in assuming the state of oxyhæmoglobin, appropriates, under normal conditions, all the oxygen it can carry. Is the proportion of hæmoglobin in the red corpuscles increased in order to correspondingly augment their carrying capacity? The suddenness with which some drugs—amyl nitrite, for example—produce active stimulation precludes such a deduction.

Does the serum itself take up oxygen in the lungs? The presence of suprarenal secretion in the serum would alone render this possible; but so little oxygen can be obtained from blood-plasma with the air-pump that the idea seems hardly

worth considering. Still, we have seen how marked is the affinity of the suprarenal secretion for this gas and mechanical means might prove quite inadequate to dissociate them when united. Again, the secretion is first poured into the vena cava and there dissolved in the serum of its venous blood. Thoroughly mixed with the latter when passed through the heart, owing to the conformation of the cardiac valves, the musculæ tendineæ, etc., it must find in the serum a normal vehicle at least during its presence in the prepulmonary vascular channels. Does the serum beyond the lung still contain suprarenal secretion? We have seen that such is not the case. Indeed, its remarkable affinity for oxygen would hardly permit it to pass through these organs and be exposed to the air therein without its becoming oxidized, or at least converted into some combination in which both the secretion and the gas would lose their individual identities.

We must not overlook the fact, however, that this combination, to satisfy the needs of our inquiry, would have to assume active functions. Again, the secretion and its extrapulmonary oxygen-laden successor would have to be antagonistic to fulfill physiological needs. In other words, before reaching the lungs the secretion would possess a marked affinity *for* oxygen, while the extrapulmonary compound would show a correspondingly marked tendency to *part with* its oxygen when bodies endowed with greater affinity for this element would be brought into contact with it.

Have we any ground for the belief that such an oxidizing compound exists in the blood? An analytical study of this question is necessarily a somewhat arduous one, but, fortunately, direct evidence is not lacking: evidence that combines the advantages of absolute reliability and at the same time covers the field with sufficient fullness to warrant judicious deductions. The paper to which we refer is that of Salkowski, already quoted, and which includes, besides his own researches, the results of those of Schmiedeberg, Jaquet, and Abelous and Biarnés.

In order to trace the connection between the observations of these investigators and our views in respect to the part played by the secretion of the adrenals in the process, it is

necessary to outline them rather fully. An editorial review of Salkowski's contribution,[1] given below,[2] so ably presents all the data necessary to our analysis that it will be utilized for this purpose. The fact that Salkowski's contribution itself in no way refers to the adrenals or their functions makes it all the more valuable, since the evidence submitted cannot even be said to have been garnered for use, or with a preconceived idea of the purposes to which it would ultimately contribute so much weight.

The review of Salkowski's paper is as follows: "In 1892 Jaquet took up the experiments, begun by Schmiedeberg in his laboratory, upon oxidation by living tissues, using as oxidizable agents those recommended by this author,—namely: benzilic alcohol and salicylic aldehyde,—because these substances, under ordinary conditions of the body-temperature, did not burn in air, while easily consumed in the organism; and because the oxidation products could only arise from them. Besides, they could under all circumstances be easily found and determined quantitatively.

1. "Jaquet at first confirmed the conclusion of Schmiedeberg, that blood alone could oxidize benzilic alcohol and convert it into benzoic acid in extremely small quantities, but he concluded that it could not oxidize salicylic aldehyde. His researches with organs also confirmed Schmiedeberg's view that benzilic alcohol and salicylic aldehyde, dissolved in the blood, are easily oxidized into benzoic acid by living organs. The remarkable data thus acquired may be summarized as follows:—

2. "The presence of blood is not at all necessary to insure oxidation through the organs, especially the lungs, so often used for this purpose; *oxidation is more perfect when, instead of blood, blood-serum is used.*[3]

3. "Pulmonary tissue poisoned with *quinine and carbolic acid* acts just as well as oxidizing agent as intact lung; hence *the oxidizing power cannot be a property of living protoplasm.* Lung acts perfectly as oxidizant even after remaining in a

[1] Salkowski: Virchow's Archiv für path. Anat., Jan. 4, 1897.

[2] Archives Générales de Médecine, March, 1898, signed "Cart."

[3] All italics are our own.

freezing mixture twenty-four or forty-eight hours, and when frozen as hard as a board.

4. "Horse- lungs and kidneys preserved twelve to fourteen days in alcohol at 75° C. unmistakably give benzoic acid or salicylic acid *after soaking in a NaCl physiological solution*, when treated as customary in experiments; this is also the case when the organs are not preserved in alcohol *in toto*, but previously reduced to a magma, then hardened in alcohol.

5. "Oxidation of benzilic alcohol and salicylic aldehyde can be caused, in weak NaCl solution, by extracts of horse- lung and kidneys. This is even possible when the organs, after having been treated two hours before with alcohol and ether, are then washed in salt-water, and also when the extracts are treated with blood containing salicylic aldehyde.

6. "Organs treated with alcohol and ether gave, all else being equal, less salicylic acid than fresh organs; still, the extracts possessed the property of *transferring the oxygen of the air to salicylic aldehyde:* a property which is totally absent in the case of simple alkaline solutions.

7. "That in this oxidation the action of a ferment or enzyme prevails is proven by boiling the organs: *i.e.*, ebullition causes entire loss of the oxidizing power.

8. "Jaquet's conclusion that blood alone cannot cause oxidation of salicylic aldehyde into salicylic acid somewhat contradicts the results of some of Salkowski's older experiments. Indeed, one year before the publication of Schmiedeberg's first work (1882) he had obtained *oxidations from blood alone;* so that Jaquet's proposition is valuable in that it confirms these older experiments.

9. "This oxidizing power of blood alone, pointed out by Salkowski in 1881, was recently confirmed by Abelous and Biarnés.[4] These authors so disposed their experiments as *to insure the passage of atmospheric air through the blood* treated with salicylic aldehyde.

10. "In his older work Salkowski *attributed this oxidizing power to the blood-corpuscles*, which he thought were the carriers of oxygen; *he now believes that this idea can no longer prevail*,

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[4] Abelous and Biarnés: Archives de Physiologie, vol., 1895.

since Abelous and Biarnés succeeded in causing oxidation of salicylic aldehyde by means of *blood-serum:* that is to say, *blood absolutely deprived of its corpuscles.*

11. "It is thus possible to say that *the blood acts as an oxidizant precisely in the sense indicated by Jaquet: i.e., through the soluble oxidation ferment it contains.* In order *to induce oxidation by means of blood, the experiments must be performed under the most favorable circumstances for oxidation, either by reducing the blood or by the continuous passage of a current of air.* Herein lies the great difference between the results obtained on the one hand by Schmiedeberg and Jaquet, and by Abelous and Biarnés on the other.

"The experiments that form the original part of the article were performed with mixtures of organs, or with their extracts (with or without blood), left during a fixed length of time in contact with salicylic aldehyde; then the salicylic acid formed was determined by means of colorimetry with the weak solution of perchloride of iron. The number of experiments performed was twenty-three.

12. "The next experiments were instituted to show that the oxidizing body is destroyed by boiling, showing it to be a ferment. It is also destroyed by remaining three days in absolute alcohol.

13. "It is important to note that, in a certain number of experiments, the quantity of salicylic acid formed was much less than in others. *Many factors certainly influence the results: abbreviation of the digestion period, the individual peculiarities of the animal, its age, its previous diet,* the time elapsed since its death, etc.

14. "A result of these various experiments is to confirm the opinion advanced by Jaquet, that *the presence of cellular protoplasm is absolutely superfluous,* and that oxidation is much more likely to be caused by a ferment soluble in water and originating in protoplasm, able also to stand a short treatment with absolute alcohol, but which, if prolonged, completely destroys it, as in the case of pepsin, for example.

15. "It is interesting to ascertain now how the oxidation property behaves toward various tissues. Muscular tissue was first examined, because it stands first as to quantity in the

organism, while from the standpoint of oxidation it presents features of special interest. . . . These experiments showed that oxidizing power of muscular tissue was extremely small." Various experiments, which need not be considered in detail here, showed that 100 grammes of each of the following organs gave salicylic acid as a result of the reaction produced with salicylic aldehyde, corresponding with the number of milligrammes opposite their names: Liver, 0.138 milligrammes; spleen, 0.110 milligrammes; kidneys, 0.022 milligrammes; pancreas, 0.0028 milligrammes; muscles, 0.0014 milligrammes.

. . . . . .

16. "Does the soluble oxidation ferment play any significant rôle during life? That such must be the case is revealed by the *great number of substances upon which the action of the oxidation ferment is exercised.* If the aromatic series is first considered, especially the benzol derivatives, a large series of known bodies is found, which, incorporated into the organism, are oxidized therein; for example: methylbenzol, ethylbenzol, propylbenzol, benzilic aldehyde, benzilic alcohol, acetophenol, which are oxidized into benzoic acid, salicylic aldehyde into salicylic acid, xylol into toluic acid, benzol into phenol, etc. . . . The question whether the action of the oxidation ferment manifests itself in physiological combinations is one of very great interest.

17. "Salkowski showed long ago that phenylpropionic acid is a regular product of albuminous disintegration by putrefaction bacteria. He even found that this acid, in the body, is oxidized into benzoic acid up to its last remnants, and that the latter leaves the organisms by uniting with glycocol in the form of hippuric acid. . . . Is the oxidation ferment capable of causing this oxidation? Salkowski's experiments have not as yet furnished an answer to this question, so that, until further data are obtained, it may be said that the bodies of the aromatic series which can be oxidized by the oxidizing ferment are limited to benzilic alcohol, salicylic aldehyde, and benzol, all bodies which do not occur physiologically in the organism.

18. "The action of the oxidation ferment on fats is better known than that on aromatic substances. Pohl has proven that

animal organs, especially the liver,—owing to its contained oxidation ferment,—were able to oxidize formaldehyde and methylic alcohol into formic acid. The action of the oxidation ferment upon glycose is well known, as also the researches of Claude Bernard, renewed by Lépine, who attributes the oxidation of the sugar in the blood to the action of a special ferment: the "glycolytic ferment." Spitzer[5] has since shown that this property of destroying sugar did not belong to the blood alone, but that it was a general attribute of protoplasm, though concerned in no way with the life of the latter. In fact, the glycolytic property still exists in old and dry extracts of organs. It is therefore very probable that *the sugar-destroying ferment which only acts in the presence of oxygen is identical with the tissue-oxidizing ferment.*"

To show the true importance of these researches, their exact bearing upon our analysis must be clearly defined. Especially important is it to realize that the experiments referred to were performed *outside* the body, the tissues being used as sources of oxygen, whereas our analysis, on the contrary, applies to reactions *within* the body, where the tissues *take up* oxygen and use it in their metabolism. In the case of the blood-serum, however, these *extra corpore* experiments give a true picture of the *intra corpore* function, since we are dealing with an *oxidizing* ferment. The chemical bodies referred to, therefore,—salicylic aldehyde, benzilic alcohol, etc.,—faithfully represent poisons that have reached the circulation, while the main process of more or less complete neutralization to which they are submitted is correspondingly portrayed by their conversion into salicylic acid, benzoic acid, etc. In other words, they do in the body what the experiments showed them to do outside the body: *i.e.*, they take up a part of, or all, the oxygen of the oxidizing ferment, *for which the serum acts as a vehicle or menstruum.* Reducing the process to its simplest expression: both, tissues and poisons, act as reducing agents upon the oxidizing compound.

A critical analysis of Salkowski's paper clearly shows that all the attributes necessary to such a process as that just

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[5] Spitzer: Berliner klin. Wochenschrift, No. 42, 1894.

defined obtain: The third and thirteenth paragraphs show that it is not the tissues that oxidize poisons, while the tenth as forcibly demonstrates that this function cannot be attributed to the blood-corpuscles. That the blood-serum contains the oxidizing principle is confirmed by Paragraphs 2 and 10. That the process can be exercised notwithstanding the alkaline salts of the serum is emphasized in Paragraph 4.

The exposure of the suprarenal secretion to the air of the lungs as the intermediate function upon which the acquisition of oxidizing powers depends is typified by the need of a continuous current of air,—*to sustain the oxidizing power of the ferment,*—referred to in Paragraph 11. That a "great number of substances upon which the action of the oxidation ferment is exercised" exist, is evident, judging from those given in Paragraph 16 and elsewhere in the paper. Finally, that there exists an underlying cause for fluctuations in the oxidizing power of the serum, digestion, age, diet, etc.,—all features which more or less influence the adequacy of the suprarenal glands,—is demonstrated in Paragraph 11. As several chapters will contribute abundant evidence to demonstrate the existence of an oxidizing substance, we will limit ourselves, for the present, to a single class of affections in which its action is clearly marked: *i.e.*, those ascribed to "uric acid."

The older view as to the origin of uric acid—*i.e.*, that it was, as held by Liebig, Wohler, and Frerichs, a product of albuminoid decomposition and a preliminary process to the production of urea—no longer prevails. Benecke, in 1874, showed that the greater part of the urea eliminated did not originate from oxidized uric acid, while Horbaczewski, in 1891, found that, just as the nuclein of pus-cells and that of the blood-corpuscles of birds could produce hypoxanthin, guanin, and xanthin, as noted by Kossel, so could it produce uric acid *in vitro* under the effects of *marked oxidation.* Nuclein administered to animals is, moreover, known to increase the production of uric acid: a fact which led Horbaczewski to conclude that normally-eliminated uric acid originates from nuclein, which in turn is liberated through the destruction of cellular structures and especially of leucocytes. This investigator further noted that leucocytosis was attended with increased elimination of

uric acid. These results were sustained by Kuhnau, who observed that pure nuclein administered in large doses was eliminated in the form of uric acid, and further confirmed by Weintraub, Umber, and Mayer after a series of counter-experiments.

Dunin and Nowaczek[6] studied the question from another direction: *i.e.*, in five cases of pneumonia, in which disease, as we have seen, leucocytosis is very marked. They found that the quantity of uric acid eliminated rises greatly the day before the crisis: *i.e.*, when absorption of the exudation and destruction of the leucocytes begin. Immediately after the crisis the uric-acid ratio rose to three times that of the precritical period, and continued high several days. It seems plain, therefore, that uric acid originates from nucleins, which in turn are decomposition products of the cells of the organism and particularly of leucocytes.

The nuclein derivatives,—hypoxanthin, guanin, xanthin,—just referred to and another, adenin, of the same class have since been termed "alloxuric bases" by Kossel and Kruger, but E. Fischer, after exhaustive investigations, traced them all to a carbon-hydrogen nucleus, the *purin* nucleus, from which many important derivatives—uric acid, caffeine, theobromine, etc., besides the nuclein bases mentioned above—can be obtained. This feature obviously demonstrated a close chemical relationship between these bodies and various substances—cocoa, coffee, tea, meats, sweet-bread, liver, and others rich in nucleins, and normally led to the conclusion that articles of food which had long been associated pathogenically with the production of uric acid, could also act as sources of nuclein bases. This was confirmed by experiments in healthy subjects, from whose urine the latter were obtained daily in varying proportions.

It then became a question as to which of the two sources of nuclein prevailed: *i.e.*, whether they were derived from body-cells, leucocytes, etc., as thought by Horbaczewski, or from articles of food, as thought by Fischer. Experimental data in

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[6] Dunin and Nowaczek: Zeitschrift für klin. Med., Bd. xxxii, 1897.

favor of Horbaczewski's view have steadily accumulated, while Fischer's position has as steadily gained ground. The prevailing view, therefore, is that the alloxuric bases are derived from the nucleins of which the body-cells, and particularly leucocytes, are the source, and also from certain articles of food. This constitutes but a subdivision of general metabolism: *i.e.*, that recognized as "nuclein metabolism."

Again, Horbaczewski, in a series of experiments, observed that splenic pulp, allowed to digest several hours with blood at the body-temperature, gave rise to a marked increase of uric acid and nuclein bases, but that the relative amounts of these products depended entirely upon the *degree of oxidation.* When simple decomposition prevailed, the nuclein bases were found to predominate, while the more advanced oxidation processes led to the formation of uric acid. That the production of uric acid must be an advanced stage of the processes through which the waste-products are prepared for excretion is thus made probable. This is sustained by the high relative proportion of oxygen—higher even than urea: $(NH_2)CO_2$—which its formula indicates, and the gradual progression toward this high proportion which the alloxuric bases show: *i.e.*, guanin, $C_5H_5N_5O$; hypoxanthin, $C_5H_4N_4O$; xanthin, $C_5H_4N_4O_2$; and uric acid, $C_5H_4N_4O_3$. Feeding with bodies rich in nucleins, spleen-pulp, thymus, etc., causes a proportionate increase of the most advanced of the alloxuric bodies, uric acid, and in health the greater part of the nitrogen of the nuclein metabolism is excreted, not as nuclein bases, but as uric acid. All these facts tend to show that *uric acid is not only the normal end-product of nuclein metabolism, but also the most highly oxidized of the alloxuric bodies.*

If this conclusion prevails, what is the utility of the oxidation of alloxuric bases? This soon appears when their toxicity, as compared to that of uric acid or urea, is realized. *Uric acid, notwithstanding the prevailing belief to the contrary, is chemically harmless.* It has been fed to animals or injected into their blood in very large doses without giving rise to untoward symptoms. Even its continued administration has failed to bring about the least pathological change in the structures which it is generally thought to assail, as shown experimentally

by A. C. Croftan.[7] True, it may have been found in very marked quantities in the serum of some gouty subjects during the active stage, as observed by Garrod; but, if the acute symptoms of this disease are due to uric acid, why do they not appear in such conditions as leukæmia, in which uric acid is also present? Uric acid is insoluble in the body-fluids, and, if it irritates the renal structures at all, it can only do so through the asperities of its crystals, since as a chemical body it is innocuous. Even the view that gouty disorders should be ascribed to its influence alone hardly stands, since Pfeiffer and Vogel and other investigators have found that the proportion of uric acid, when ascertained by modern methods during or between attacks of gout, shows but little variation.

Urea is also a benign substance; Bouchard found in a series of painstaking experiments that it was even less toxic than sugar. Whereas it took 2.5 grammes of bicarbonate of soda to kill 1 kilogramme of animal, from 5.5 to 6.3 grammes of urea were required to reach the same result. Water and normal albumin alone, of the animal fluids, are less toxic than urea. As to its influence on the kidneys, Bouchard was led to conclude that, although a product of disassimilation, it played a useful rôle in the economy as a diuretic.

Quite another story is unfolded, however, when the alloxuric bases are analyzed from the same standpoint. As products of worn-out nuclei which have served their purpose in elaborating blood-corpuscles, both red and white, and other cellular elements, their effects are those of powerful alkaloids. Readily soluble in the relatively large proportion of menstruum which the body-fluids afford them, they are carried in all directions, and become the source of the various phenomena usually ascribed to "gouty diathesis" and now credited to them by the more recent writers. Gaucher[8] and Kolisch,[9] in the order named, long ago referred to the alloxuric bases—xanthin, hypoxanthin, adenin, and guanin—as violently toxic agents, while Levison ascribes to them the renal lesions which are

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[7] A. C. Croftan: Journal of the American Medical Association, July 8, 1899.

[8] Gaucher: Thèse de Paris, 1884.

[9] Kolisch: Wiener med. Wochenschrift, 1895; quoted by F. Levison, "Sajous's Analytical Cyclopædia of Practical Medicine," vol. iii.

invariably found post-mortem in gouty subjects. The pathogenic effects of these bodies have since then been emphasized by several investigators, including Croftan,[10] who, in a series of experiments, observed that "both xanthin and hypoxanthin, when injected hypodermically in the strength of a 0.3- to 0.7-per-cent. watery solution for a period of several months, produced granular degeneration of the epithelial cells lining the tubuli contorti and a proliferation of the endothelium of the intertubular capillaries." He also found, in confirmation of the observations of Charcot, Binet, Coën, and d'Ajutolo, that the renal lesions of chronic lead intoxication—which, as shown by Garrod, Lancereaux, and others, is one of the etiological factors of gout—are identically those caused by alloxuric bases.

The non-toxic nature of uric acid and of urea, the violent toxicity of the alloxuric bases, and the relative position of uric acid to the latter, as the most highly oxidized body of the series, seem fully to justify the view that *the alloxuric bases are converted from physiological toxics to uric acid, an inert body, by oxidation.*

If the functions of the suprarenal glands are what they are said to be in this work, the classical experiments of Minkowski, which showed that uric acid was almost entirely formed in the liver, lose much of their weight. As will be remembered, this investigator kept geese alive from six to twenty hours after extirpation of the liver; their urine was then found to contain but 2 or 3 per cent. of uric acid instead of the normal 60 or 70 per cent. If large doses of poisons produce sudden suprarenal insufficiency, it is evident that the removal of so important a toxic destroyer as the liver should promptly cause in the system an accumulation of catabolic products amply sufficient to overwhelm the adrenals in a short time. Not only are Minkowski's experiments invalidated by this fact, but all others performed since in which, by diverting the blood from the liver into other channels, kindred results were reached. This does not, however, eliminate the liver from the field of activity; indeed, it takes a part in the protective process commensurate with its position among organs as a

[10] Croftan: *Loc. cit.*

storehouse for oxygen, with the spleen, also remarkable in this particular, as a close second. But the kidneys do not in the least appear to stand, as thought by many, in the light of uric-acid forming organs, but, on the contrary, as the main organs to be protected, since it is upon their tissues that the brunt of the disorganizing effects of the alloxuric bases is exercised. "We are indebted to Levison[11] and others for the knowledge that granular atrophy of the kidneys is a constant precursor of gout," says Croftan.[12] Such a morbid process would precisely coincide with the effects upon renal tissues that free alloxuric bases would be expected to produce.

Yet, the labors of Garrod, Luff, and others have emphasized the fact that uric acid is not present in the blood during health either in mammals or birds. This is difficult to reconcile with the view that the kidneys are not uric-acid-forming organs, since its presence in the urine exceeds in quantity that of the alloxuric bodies. But, according to von Noorden,[13] the Heintz method of ascertaining the presence of uric acid in the blood is so faulty that Garrod's painstaking analyses and those of the many able successors have lost all scientific value in this particular. Bouchard, Sprague, Pfeiffer, Vogel, and Croftan, on the other hand, using more modern methods, have invariably found uric acid in normal blood, thus indirectly eliminating the kidneys as the uric-acid-forming organs.

Haig's faithful work in this direction must not be overlooked. While his view that uric acid is the source of the manifestations of toxicity witnessed is not sustained by modern research, his numerous analyses distinctly prove two points which modern experimentation has fully upheld: *i.e.*, that the uric acid found in the urine is a fluctuating quantity, and that various foods are capable of augmenting this quantity. The kidneys once eliminated from the depurative process, we are relegated to the blood as the main source of the uric acid, and therefore to the blood as the seat of the reaction, which consists in the conversion of varying quantities of toxic alloxuric bodies into equally variable quantities of benign uric acid.

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[11] Levison: Zeitschrift f. klin. Med., vol. xxvi, p. 314.
[12] Croftan: *Loc. cit.*
[13] Von Noorden: Quoted by Croftan, *loc. cit.*

That the reaction through which the alloxuric bases are converted into uric acid by oxygen occurs *in the blood* may be further emphasized by Horbaczewski's experiments in an unexpected manner—unexpected in the same sense that his experiments may be used to sustain one of his important deductions and at the same time prove the presence of oxygen in the body-fluids. When in the course of these experiments the spleen-pulp and the blood were brought into contact at the normal body-temperature *in the presence of air,* uric acid was formed, while the same experiments performed after the *exclusion of air* produced alloxuric bases. Horbaczewski correctly concluded from this that the relative quantity of alloxuric bases formed as to that of uric acid depended upon the extent of oxidation. In other words, the surplus of oxygen which the presence of air afforded accounted for the formation of uric acid. That this confirms the absolute need of air, insisted upon by Abelous and Biarnés, and further sustains the view advanced in the present work, that the suprarenal secretion becomes oxidized in the lungs, is evident. We thus obtain proofs from three different directions that *the blood contains an oxidizing principle, and that the alloxuric bases are converted through this principle into uric acid.*

Brief reference must now be made to the nature of the symptoms that occur as the result of intoxication from the alloxuric bases. To state that the suprarenal glands respond to the more or less great quantities of these toxics that appear in the blood at various times during health, as the result of undue nuclein ingestion, or during disease, as the result of hyperleucocytosis, more or less marked tissue metamorphosis, etc., is to confirm what the reader has doubtless already recognized. Haig has often emphasized the high arterial tension of what he thought to be "uric-acid" poisoning; it attends migraine and the various milder disorders ascribed to the "gouty diathesis." If the postulate that "muscular vessels and capillaries are antagonistic in dilation and contraction" is recalled, we can readily account for this phenomenon, the alloxuric bases, *like any other poison,* causing contraction of the central vessels and dilation of the peripheral capillaries. The marked pallor, cold and clammy extremities and skin wit-

nessed in severe cases also typify the stage of marked poisoning: *i.e.*, of suprarenal insufficiency. That this stage may prove fatal is shown by some cases of so-called "retrocedent" gout, in which the main symptoms, according to Osler, are "pain, vomiting, diarrhœa, and great depression"—or "cardiac manifestations—dyspnœa, pain, and irregular action of the heart." In acute gout, immediately before an attack, "the patient complains," says Levison,[14] "of headache, vertigo, drowsiness, . . . cramps in the calves and elsewhere." He also refers to "pain in the various articulations; paræsthetic sensations, such as numbness of the fingers, chilliness, etc.,"—all signs which point directly to the suprarenal glands. We can legitimately conclude, therefore, that *the adrenals react under the effects of the alloxuric bases precisely as they do under those of any other toxic: i.e., toxins, mineral and vegetable poisons, venoms, etc.*

Such is the process through which probably the most active oxidizable poison produced in the organism is neutralized. In a perfectly healthy subject the equilibrium of production and destruction is constant, and the suprarenal glands hardly, if at all, assert their presence through their characteristic symptoms. A benign acid is produced and continuously eliminated, the physiological cycle being performed without interruption, and symptomatic fluctuations only occur when increased tissue metamorphosis, as a result of exercise, digestion, etc., bring on an increase of the physiological work of which the adrenals are the primary source. Kindred reactions, of which the oxidizing substance in the serum is probably the basis, are brought about by the ingestion of certain fruits,—green gages, cranberries, and prunes, for instance,—hippuric acid being then found in the urine in greater quantities than usual.

The application of the physiological function of which the oxidizing substance is the active agency to poisoning from external poisons is well illustrated by the fact that, when certain agents or poisons are ingested,—toluol, benzylamin, benzoic acid, cinnamic acid, oil of bitter almonds, etc.,—the ex-

[14] Levison: *Loc. cit.*

cretion of hippuric acid is likewise increased. This is also witnessed in acute febrile processes, diabetes, chorea, and various other disorders. On the whole, the following conclusions appear to us to be sustained:—

1. When the secretion of the adrenals reaches the pulmonary alveoli, it absorbs oxygen from the air and forms with the latter a compound, or "oxidizing substance."

2. A part of this oxidizing substance is absorbed by the hæmoglobin of the corpuscles and the balance remains in the blood-plasma.

3. This oxidizing substance is the reagent to which the oxidation processes that occur in the blood-stream are due.

The far-reaching meaning of the third conclusion will be emphasized in subsequent chapters, which in reality constitute a continuous chain of evidence to the effect that the oxidizing substance underlies all the oxidation processes of the organism.

CHAPTER IV.

THE INTERNAL SECRETIONS OF THE THYROID AND THYMUS GLANDS IN THEIR RELATIONS TO THE ADRENALS.

THE THYROID GLAND AND THE ADRENALS.

A FEW years ago Robert Hutchinson[1] closed a review of the literature upon the effects of thyroid extractives on metabolism with the following remark: "Briefly, then, it may be said that the effect of the administration of the thyroid is to increase oxidation in the body; it makes the tissues, as it were, more inflammable, so that they burn away more rapidly. The products of the disintegration of the nitrogenous tissues appear in the urine almost entirely in the form of urea, uric acid, the xanthin bases, being neither regularly nor appreciably increased, while the products of the fat-destruction are eliminated as CO_2 by the lungs, and water by the kidneys." Recent investigations have but confirmed these deductions.

On the other hand, there is considerable uncertainty in respect to the physiological rôle of the thyroid. This is well exemplified in the following lines by Professor Foster[2]: "When in certain animals (monkeys, dogs, and other *carnivora*[3]; and the same has been observed in man) the gland is extirpated, even with the greatest care, the operation is frequently followed by the occurrence of peculiar nervous symptoms, such as *muscular twitchings* and *tremors*, *spasms*, and even *tetanic* convulsions (more especially observed in young animals), accompanied or succeeded by irregularity or failure of voluntary movements; subsequently there may ensue varied symptoms which may be described under the general term of disordered nutrition, ending eventually in death. In a *certain number* of cases, however, in the above kinds of animals, no serious symptoms follow, even the *total* extirpation of the organ pro-

[1] Robert Hutchinson: British Medical Journal, July 16, 1898.
[2] Foster: *Loc. cit.*, 465.
[3] The italics are our own.

ducing no marked effect; and in rabbits and other *herbivorous* animals removal is said never to be followed by any of the above results. It has been urged that the symptoms, when seen, are the effects not of the mere absence of the organ, but of the mischief set up by the operation in adjoining structures, more especially in the laryngeal nerves and vagus trunks; but this does not seem a valid explanation. If, as suggested above, certain metabolic processes are normally going on in the organ, we may fairly suppose that, in the absence of the organ, the interruption of the normal sequence of chemical change would throw upon the circulation certain strange substances which, acting like a poison, might produce the nervous symptoms, throw into disorder the nutrition of various tissues, and finally bring about death. We may further explain the cases where symptoms are absent by supposing that, for some reason or other, "things have taken a different turn": the particular poisonous substances have not made their appearance, but innocuous ones have taken their place; and we know how slight a change in chemical composition may turn a poison into an inert body. This, of course, remains a mere supposition until we can state what the exact metabolic processes are, and name the substances which work the mischief; but it seems more reasonable to accept such a provisional supposition than to conclude that the thyroid may be removed without producing any effect whatever on the organism. An animal without a thyroid may appear perfectly well, because the circumstances to which it is exposed do not happen to test the imperfection from which it is really suffering, just as a man's inability to swim may not be apparent until he happens to fall into the water. The animals which do succumb to the operation of removal of the organ are, for some reason or other, put to the test, and are found wanting. The very discordance of the experimental results points to the physiological moral that the phenomena which we are as yet able to observe form, as it were, a mere surface covering intricate processes *at present wholly, or nearly wholly, hidden from us.*"[4]

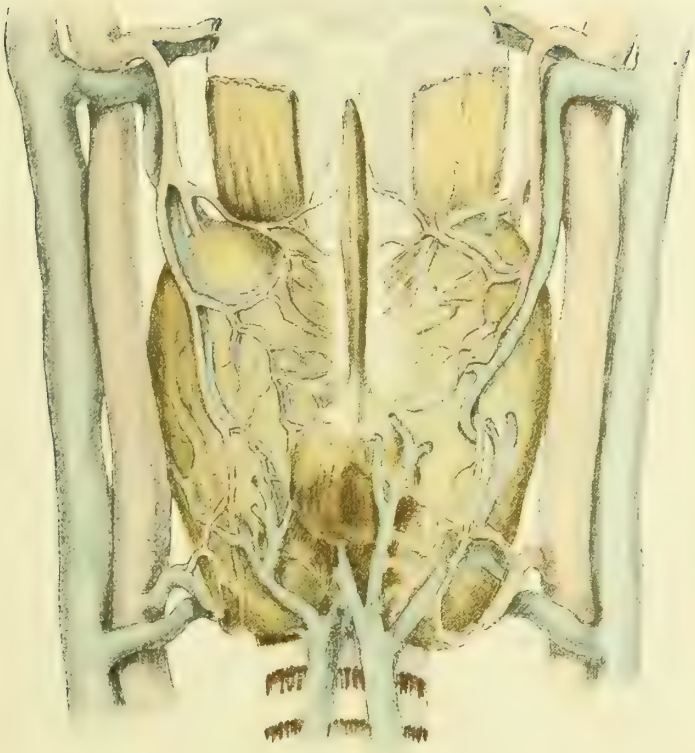
If the data recorded in the last chapter concerning the

[4] The italics are our own.

direct causal relationship between the adrenals and oxidation processes are sound, the thyroid must either be considered as capable of playing a similar rôle in the organism, or it must be so related to the adrenals as to, in a measure, govern their functions. Analysis of the former proposition promptly shows that it cannot prevail. As to any relationship between the thyroid and the adrenals, all that can be said is that there seems to exist a certain degree of functional connection between them, judging from the effects of their removal and the character of their blood-supply. Indeed, the arteries of the thyroid are remarkable in various ways, and particularly for their number and size. Luschka[5] has estimated that the sum of their transverse section equals the sectional area of the internal carotid artery of the same side, so that nearly as much blood passes through the four arteries supplying the gland as goes to supply the brain through the vertebral and internal carotid artery. The veins are correspondingly large, and remarkable also for their number and free inosculation. This is well shown in the annexed colored plate. Collecting, as they do, the great mass of blood passed through the organ, they are found to empty into channels that are suggestive by their immediate anatomical relations: the internal jugular and the innominate veins, which ultimately empty their blood into the superior vena cava. Here again, therefore, we find a loop with a large arterial trunk as the starting-point, a vena cava as the main intermediate channel, and the heart as a common distributing mechanism. As in the case of the suprarenal secretion, the thyroid secretion must therefore penetrate the pulmonary circuit, return to the heart, and then be distributed throughout the organism with blood.

The features available as elements for an analysis of the functions of the thyroid suggest that we are not dealing with an intraglandular process having for its purpose to locally destroy toxic substances. In the first place, the demonstrated increase of vital activities, growth, metabolism, mental power, etc., which thyroid extract procures would become unintelligible, since its effect is peculiar to thyroid extractives: a fact

[5] Luschka: Allen's "Anatomy," p. 366.



VASCULAR SUPPLY OF THE THYROID GLAND.

which eliminates them from the list of poisons and indicates a direct relationship with a physiological function. In the second place, it is well known that the symptoms that occur after removal of the thyroid in animals may be arrested for a time by injections of thyroid extract, while grafting or transplanting of a gland into the peritoneum, the abdominal wall, or elsewhere may arrest them completely. Christiani,[6] in a series of experiments on reptiles and mammalia, found that properly transplanted thyroids continued their functions, and that they preserved their morphological characters without showing any tendency to atrophy. Von Erlenden[7] ascertained that such glands continued to produce their colloid material and formed new vascular connections,—all facts which Schiff, Horsley, von Eiselsberg, Canizzaro, and many others had already noted. Christiani also[8] ascertained, by means of microscopical examinations of fragments of transplanted organs, repeated at short intervals, that vascular regeneration of the gland occupied three months.

Again several experimenters have successfully performed transplantations in carnivorous animals,—cats, dogs, etc.,—which, we have seen, often die after thyroidectomy. How could we account for the absence of even marked symptoms in these animals during the prevascular period—*i.e.*, that ensuing between the date of transplantation and the third month—if the thyroid had for its mission to destroy toxics *in situ?* If the function of the organ is to destroy these bodies within its own structures, can we reasonably expect the insignificant quantity of blood which then courses through the transplanted organ to satisfy the needs of the function? In order to carry it on satisfactorily the entire blood would have to course through the grafted thyroid, whereas even when the organ is in its normal position in the neck, only a comparatively small proportion of the blood of the organism passes through it notwithstanding its large vascular supply. On the other hand, we can easily understand how immediate benefit could be ob-

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[6] Christiani: Revue Médicale de la Suisse Romande, Dec. 20, 1900.

[7] Von Erlenden: Centralblatt für d. Grenzgebiete der Medicin und Chirurgie, Nov., 1899.

[8] Christiani: Archives de Physiologie, Jan., 1895.

tained from a transplanted thyroid brought into contact with a raw surface prepared for its reception, through *absorption into* the blood, not necessarily of a secretion at first, since the glandular functions would then be in abeyance, but of the glandular juices themselves, which have been found so remarkably active in cretinism, myxœdema, etc.

We are brought nearer to the suprarenal glandular functions when the symptoms usually referred to as "nervous" are reviewed. The "muscular twitchings and tremors, spasms, and even tetanic convulsions" remind us vividly of the stage of stimulation of the adrenals, though they occur as results of *removal* of the thyroid. That the functions of the thyroid must be connected with the destruction of toxic elements of internal origin is evident. Yet if its secretion enters the circulation and enhances metabolic processes and oxidation, and since it is not itself endowed with properties that enable it to directly carry on such a process as stated, it can only do so indirectly. In view of the data incorporated in previous chapters, may the thyroid gland not supply the blood with some agency through which, directly or indirectly, the suprarenal glands are stimulated?

Removal of the thyroid in rabbits and other herbivorous mammals and birds is not followed by the above-mentioned symptoms, whereas these are prominent in the carnivora: the dog, cat, monkey, man, etc. Still, the so-called nervous disturbances do not *always* occur in the latter: a fact which has caused some authoritative physiologists—Munk, of Berlin, for instance—to conclude that the thyroid was not an organ of extreme importance to life. In his experiments 50 per cent. of monkeys and rabbits and 25 per cent. of dogs and cats remained unaffected notwithstanding the ascertained absence of accessory organs. Cunningham,[9] in a series of very carefully conducted experiments, also found that the ingestion of some tissues—thymus, muscle, etc.—produced symptoms strikingly similar to those observed in the thyroid intoxication, and concluded that the latter cannot, therefore, be looked upon as due to a specific derivative of the thyroid gland. Unlike Munk,

[9] Cunningham: Journal of Experimental Med., March, 1898.

however, he found that fresh thyroid and thymus extractives were capable of relieving for a time the symptoms of acute cachexia in young dogs from which the thyroid had been removed.

While these observations have been considered as opposed to prevailing views, they lose this characteristic when the suprarenal glands are looked upon as connected, though passively, with the toxic manifestations observed. The thyroid may not necessarily be an organ of extreme importance to life, for instance, as thought by Munk, since it thus becomes the source of a substance which is merely intended to stimulate the adrenals: *i.e.*, to produce effects similar to those of a poison upon them or their center precisely as did the many drugs we have reviewed. In the animals in which acute cachexia did not occur in Munk's experiments the adrenals were simply adequate to meet the extra call upon their functions, while in those that succumbed—the majority—the adrenals yielded to accumulated waste-products, owing to the suprarenal insufficiency engendered. So was Cunningham right in saying that the symptoms of intoxication could not be ascribed to the specific thyroid derivative, since all the toxic symptoms observed, whether obtained from tissue toxalbumins, thyroid extract, or any other active body, can now all be traced to the adrenals.

Under these circumstances it is obvious that continued administration of thyroid extractives should so stimulate the adrenals as to enable them, through overactivity, to increase the oxidizing substance in the serum and destroy the toxic waste-products. Baumann and Goldmann[10] found that thyroidectomized dogs did not show tetanic convulsions as long as iodothyrin was administered regularly each day in doses ranging from 2 to 6 grammes, but the convulsions returned as soon as the iodothyrin was no longer administered. A striking reminder of the effects of antitoxic serum is the fact that the more marked were the symptoms and the longer was the administration of thyroid delayed, the larger had the dose to be to counteract the phenomena witnessed. This simul-

[10] Baumann and Goldmann: Münchener med. Wochenschrift, p. 1153, 1896.

taneously confirms the enormous mass of clinical evidence accumulated in recent years as to the value of thyroid extract and accounts for the contradictory evidence recorded. The features that have remained unrecognized, however, provided the views advanced herein are sound, are:—

1. That the symptom-complex termed "cachexia strumipriva," though of thyroidal origin, is a direct consequence of adrenal insufficiency.

2. That the thyroid gland is but an auxiliary organ to the adrenals, in that it supplies the blood with a secretion which directly or indirectly increases the adrenal secretory functions and thereby augments the activity of oxidation processes.

EXOPHTHALMIC GOITER AND IMPAIRED FUNCTIONAL ACTIVITY OF THE ADRENALS.

The relationship between the adrenals and the thyroid soon asserts itself when we transfer the analysis to the diseases that are ascribed to excessive or insufficient thyroid secretion: interpretations that are fairly exact, but which nevertheless would now convey any meaning other than that generally accorded them. Exophthalmic goiter at once suggests itself in this connection. Instead, however, of attributing the phenomena witnessed to the immediate action of an excessive amount of thyroid secretion upon the organism at large, it now seems more exact to ascribe them to excessive and continuous, direct or indirect, stimulation of the adrenals produced by the corresponding excess of thyroid secretion.

To demonstrate the existence of such a causal relationship, however, the symptoms of this disease should be shown to vary in a measure as they do when external poisons are introduced into the blood. A relatively small excess of thyroid secretion should also produce symptoms of suprarenal overactivity, while a large excess should give rise to signs of insufficiency. All these features are clearly sustained by the semeiology of this affection:—

Adrenal overactivity is exemplified by: 1. The cerebral hyperoxidation, as manifested by headache, irritability, excitability, capriciousness or unnatural gayety, hallucinations, mania, and epileptic convulsions. 2. The unusual muscular

metabolism and consequent muscular fatigue,—also due to excessive oxidation,—as manifested by the fibrillary tremor similar to that of excitement and to be distinguished from the paretic tremor, the painful cramps in the extremities, the reduced chest-expansion, the tetanic spasms of the hands, and general emaciation. 3. The contraction of central and other muscular vessels and centrifugal dilation of the capillaries, as manifested in the brain by the signs just referred to; in the peripheral tissues by cutaneous flushing and superficial heat, urticaria, erythema, purpura, localized and general œdema; and in the deeper organs by dyspnœa, dry cough, epistaxis, and hæmoptysis as to the respiratory organs; salivation, vomiting, intense thirst, capricious and often ravenous appetite to compensate for the excessive oxidation, as to the stomach; and the earlier retro-ocular vascular, sometimes varicose, turgescence with slight exophthalmos, flashes, sensation of pressure, and brow-ache as to the visual apparatus. 4. The increased cardiac stimulation, as shown by the rapid and violent action,—due to *cramped* heart, a condition that prevails when, as will be shown, the continued presence of poisons in the blood causes the suprarenal secretion to continuously flow in excess,—the violent action being transmitted to the carotid and other large vessels, and to the liver and spleen, which may also be felt to pulsate (cardiac hypertrophy is often found post-mortem in such cases). 5. And, finally, by the exaggerated tendon-reflex, due to excessive muscular and spinal oxidation.

Adrenal insufficiency, though not encountered in all cases, is fully as well exemplified: 1. By the cerebral suboxidation and nutrition, as manifested by the mental impotence and low spiritedness; melancholia. 2. By the reduced muscular metabolism, as suggested by the loss of strength, stumbling, paretic tremors, paralysis agitans, and finally hemiplegia and other forms of motor paralysis. 3. By the dilation of the central and other muscular vessels and passive contraction of the capillaries, as illustrated by the cerebral and muscular symptoms just referred to, the pallor and general marasmus; sweating due to relaxation of the sweat-gland muscles; alopecia; dental caries; vitiligo, leucoderma, scleroderma, and in advanced cases *bronzing;* and also by the colliquative diarrhœa

and persistent terminal vomiting, as to the gastro-intestinal tract; and glycosuria, albuminuria, acetonuria, excess of urea, as to the general metabolic processes. 4. By the eye-symptoms: the slow descent of the upper eyelids (von Graefe's sign), due to paresis of the orbicularis; increase of the palpebral fissures and infrequent winking (Stellwag's sign), due to muscular paresis *plus* exophthalmos, ascribable to paresis of the ocular muscles, and reaching sometimes to complete ophthalmoplegia. 5. By the insufficient cardiac stimulation, as shown by the weak, rapid (sometimes 200), and irregular heart-beat, air-hunger, and cyanosis (cardiac dilation with muscular degeneration is usually found post-mortem in such cases). 6. And, finally, by numerous evidences of impaired nutrition, softness of the bones, atrophy of the uterus, degeneration of the arterial walls, etc., etc.

It is important to bear in mind, in this connection, however, that the symptoms of suprarenal insufficiency are the result of an excessive supply of thyroid secretion, the suprarenal glands finally lapsing into this condition as they would under the effects of any toxic, through overstimulation and exhaustion of their cerebral centers. As is well known and as herein sustained, a deficiency of thyroid secretion gives rise to another disease: *i.e.*, myxœdema.

The above list only includes the main symptoms of the disease: *i.e.*, those that emphasize most strikingly the physiological and pathological connection between the thyroid and the adrenals. The manner in which all the symptoms of overstimulation and insufficiency of the adrenals are reproduced seems to clearly show that exophthalmic goiter is the result of an excess of suprarenal secretion, due primarily to increase of thyroid secretion.

Doubt has been expressed, however, that excessive thyroid secretion could occur as the only pathogenic factor. Thus, Ord and Mackenzie[11] contend that, "if overactivity or oversecretion of an hypertrophied thyroid gland were the whole disease, it ought to be possible to produce it by administration of large quantities of thyroid gland. No one has yet succeeded

[11] Ord and Mackenzie: Quoted by Godfrey Carter, Edinburgh Medical Journal, Oct., 1899.

in producing exophthalmos in this way." That such cases *do* occur may be shown by the following instance reported by Notthaft[12]: His patient, a man 43 years of age, had, on his own responsibility, taken thyroid extract for obesity. Not content with the slow progress witnessed at first, he increased the dose, and within five weeks took nearly 5000 grains of the extract. "For the first three weeks nothing was noticed, except loss of flesh, but after this time dyspnœa came on, with swelling of the neck and very rapid loss of weight. Altogether, thirty pounds were lost, and five-sixths of this loss took place in the last three weeks. When examined, the patient had marked exophthalmos, with both Stellwag's and von Graefe's signs; the thyroid gland was enlarged and pulsated, and there was a thrill over it. A fine tremor of the fingers and tongue was quite evident; the cardiac apex-beat was displaced outward, and the pulse was 120 to the minute; there was cough and severe mental depression; polyuria and glycosuria were also present. Under the use of Fowler's solution and after the withdrawal of the thyroid extract, most of the symptoms rapidly disappeared, only the ocular manifestations and the goiter persisting for nearly six months." We have here, not only the stage of suprarenal overactivity, including the cramped heart, as witnessed by the displacement of the apex, but also the earlier manifestations of insufficiency: mental depression, glycosuria, Stellwag's and von Graefe's signs—all features to which the gradual recovery, after withdrawal of the thyroid extract, contributes the necessary complementary evidence.

A mass of testimony could furthermore be deduced from the results of thyroidectomy. How could we account, for instance, for the cases reported by Doyen,[13] in which, after removal of the gland, followed by recovery, all the symptoms returned when they were given thyroid extract, then disappeared as soon as its administration ceased, without implicating oversecretion of the thyroid as the primary pathogenic factor of the disease? This also invalidates all the theories in which the thyroid is credited with the power of reducing toxic substances *in loco,* since the glands are *absent* in these cases and

[12] Notthaft: Centralblatt für innere Med., April 9, 1898.
[13] Doyen: Semaine Médicale, July 29, 1897.

the supposed physiological function cannot occur; it also suggests, when considered with the other data adduced, that excessive thyroid secretion, by overstimulating the cerebral centers of the suprarenal glands, as would any equally active agency, gives rise to the symptoms of suprarenal overactivity followed by symptoms of suprarenal insufficiency that have been termed collectively "exophthalmic goiter." To establish this view on a solid footing, however, other features of the problem must be considered.

What is the nature of the agency through which these phenomena are produced? Whether it be Baumann's iodothyrin, R. Hutchinson's colloid substance,—which, by the way, is very soluble in dilute alkaline fluids, such as the blood-plasma,—Fränkel's so-called thyreo-antitoxin, Oswald's more recently introduced thyreoglobulin, or any of the thyroid derivatives, the one agent upon which all their advocates depend for physiological effects is the iodine which all effective extractives contain. Yet the well-known untoward effects of this halogen when administered therapeutically in large doses—such as would be deemed necessary to produce exophthalmic goiter—would seem to suggest that there should be present in organic combination with it an agent capable of antagonizing iodism.

To counteract iodism we use arsenic. In a valuable paper Professor Armand Gautier[14] has recently shown that, while arsenic could be found in the various structures of the organism, the thyroid gland contained more than any organ, the thymus, the mammary gland, the skin, hair, and nails being next in quantitative sequence. He found it incorporated in the glandular nucleins along with the iodine. To these iodized and arsenized nucleoproteids Gautier ascribes the physiological functions of the glands, and he found that the structures which are especially benefited by arsenical treatment, the hair and the nails, are precisely among those which normally contain the most iodine and arsenic. With his pupil, Bourcel,[15] he ascertained, furthermore, that menstrual blood contained a notable proportion of arsenic and iodine. Gautier's experi-

[14] Armand Gautier: Trans. Thirteenth International Congress, 1900.
[15] Bourcel: Thèse de Paris, 1900.

ments led him to the conclusion that the bodies referred to "were continuously poured in small quantities in the lymphatics and in the blood to play therein the rôle of vitality stimulants and to enhance cell-reproduction." This thought is quite in accord with the views herein recorded, particularly those pertaining to the increased oxidation which suprarenal overactivity procures, since, after all, to increase oxidation is to enhance all manifestations of vital energy.

Yet the presence of arsenic in the thyroid introduces a source of confusion, since, as we have seen, all the toxic phenomena ascribed to poisons are of suprarenal origin, and arsenic might therefore as well be the source of the suprarenal phenomena of exophthalmic goiter as iodine, to which we have traced them. The question reduces itself to this, however: does the arsenic offset iodism as we have suggested, or does it also act as a suprarenal stimulant?

As to the connection between arsenic and exophthalmic goiter, Notthaft's case, produced by thyroid extract, suggests that a combination of these agents does not produce the disease. Since thyroid *extract* was used, we can assume that all active constituents took part in the production of the effects witnessed. With the extractives,—iodothyrin, thyreoglobulin, etc.,—however, it would seem, in view of their mode of preparation and the smaller dose administered, that in the undoubtedly active effects obtained the arsenic should count for practically nothing: a fact which would relegate all the phenomena to the action of the iodine. That such is actually the case is sustained by chemical and experimental evidence.

Mabille has observed that the untoward symptoms caused by iodothyrin, when used in the human subject as a remedy, or in experimental animals, could be reduced to a great extent and even prevented by the simultaneous use of arsenic. Experiments in dogs showed that the toxic effects of large doses did not appear when arsenic was used simultaneously, while they could be arrested by it when iodothyrin had been given alone. In the case of a goitrous woman 42 years of age, he administered this preparation in doses varying from 3 to 10 grains daily. Marked palpitations, lumbar pains, and tremor having appeared, the dose was reduced and the untoward

symptoms vanished. Iodothyrin was then administered in increased doses,—12 grains daily,—but simultaneously with 12 drops of Fowler's solution. Not a single sign of thyroidism showed itself; but, when the use of the arsenic was discontinued for three days, the toxic symptoms recurred, and again disappeared when the use of arsenic was resumed. This remarkable property of arsenic was confirmed by Ewald.[16] This investigator was not only led to grant it all the properties referred to by Mabille, but he found it to exert its antagonistic action against thyroidism far more promptly than atropine when administered to attenuate or prevent the noxious effects of potassium iodide. On the whole, we can fairly conclude that *iodine is the most active factor of the thyroidal constituents* and that *it is through its effects that the adrenals are directly or indirectly overstimulated in exophthalmic goiter.*

There is another feature of the problem which demands elucidation. Overactivity of the thyroid being accepted as the cause of exophthalmic goiter, how can we account for the undoubted cases of recovery that have occurred as the result of treatment with thyroid extract and other thyroid derivatives? When some years ago Owen reported that he had witnessed marked improvement after this treatment, it was tried on all sides, generally with unfavorable results. Since then, however, quite a number of successful cases have been reported.

These contradictory results are easily accounted for when we consider the part played by the suprarenal glands in the process, and particularly the fact that overactivity and insufficiency of these organs give rise to different, though co-related, symptoms. Interesting in this connection is a clinical observation of Solomon Solis-Cohen's, quoted as given by a reviewer[17]:—

"Dr. Cohen remarked that his experience went to show that in exceptional cases thyroid preparations might benefit goitrous patients, both those with simple goiter and those with Graves's disease; but that, as a rule, the effect was *nil* or not good. He could give no definite rule for discrimination, al-

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[16] Ewald: Die Therapie der Gegenwart, No. 9, 1899.
[17] Alienist and Neurologist, Oct., 1896.

though the effect of *temperature*[18] upon the patient might be found to be of use, it being his present impression that those who were *unduly susceptible to cold would do well*, and those who were *unduly susceptible to heat would do badly*, under treatment with thyroid preparations."

If during the stage of overactivity the central vascular trunks are contracted and the peripheral capillaries are overfilled and dilated, we can readily understand why the patient is "unduly susceptible to heat" and why thyroid preparations, by adding to the stimulation, accentuate the symptoms. A case reported by H. L. Winter[19] will serve to illustrate this fact. The patient, a woman aged 32 years, had a pulse of 160, with marked tremor and flushings, and was extremely irritable; the goiter was firm and pulsating and the exophthalmos marked. She was given thyroid extract, 5 grains daily; all the symptoms were exaggerated and she complained of severe frontal headache. The thyroid extract was discontinued, and tincture of digitalis, with a saline purgative, given; the next day there was marked relief. Ten days later thyroid extract was again exhibited, 2 $^1/_2$ grains daily. All the symptoms steadily grew worse; and at the end of two weeks the attacks of tachycardia were so violent on attempting to sit or stand that she had to keep to her bed, her pulse being 160. The extract was then discontinued and a temporary improvement followed under other methods of treatment.

The opposite result may be expected when the patient is "unduly susceptible to cold," because his central vascular trunks are dilated and his superficial capillaries contracted as the result of suprarenal insufficiency—the characteristic of advanced cases. In exophthalmic goiter, the "advanced stage" means more, however, than it does in the average disease. The first stage being due to overactivity of the thyroid, as soon as the insufficiency of the adrenals appears, oxidation becomes less active, and the thyroid, with all other organs, correspondingly so. The main source of trouble thus gradually disappears and is replaced *by another form of toxæmia, one resulting from*

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[18] All italics are our own.

[19] H. L. Winter: American Medico-Surgical Bulletin, July 11, 1896.

deficient oxidation, the immediate consequence of suprarenal insufficiency. A vicious circle is thus created; the toxic products of metabolism engender further insufficiency of the adrenals, while this condition, in turn, allows the toxics to accumulate in the organism. Finally, marasmus appears, if some intercurrent pulmonary or cardiac acute disorder does not cause death before this stage is reached. This stage of the disease includes the cases in which exophthalmic goiter and myxœdema appear jointly, since in a small proportion of instances the thyroidal secretion becomes reduced below the needs of the suprarenal glands.

It seems evident that these advanced, not necessarily grave, cases of exophthalmic goiter, should be assisted by a supply of the very agent which they now lack: *i.e.,* their normal suprarenal stimulus. A case reported by Silex[20] and characterized by Kroenig, who had seen it, as "very grave," was thus cured after taking 1200 grains of thyroid extract. All the typical signs had been present, and so advanced was the muscular weakness that the patient, a woman aged 42 years, could hardly walk. A case cured by R. Cox[21] also showed "general prostration," but the thyroid extract used was doubtless greatly assisted by the intestinal irrigations simultaneously employed. Another case successfully treated by O. Martin[22] "could not rise without experiencing great fatigue" when first seen. Another case greatly benefited by C. L. Lang[23] presented "an emaciated, tremulous, *dusky* countenance" and "was confined to bed," etc.

Another class of cases that clinical evidence shows to be benefited includes those which, through acquired or inherited suprarenal weakness, promptly yield to the primary hyperoxidation. Such cases often show signs of a quasi-myxœdema during their earlier years of life. An example of this class is afforded by Kerley.[24] The father of the patient had suffered from epilepsy and a sister had died of tubercular meningitis:

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[20] Silex: Berliner klin. Wochenschrift, No. 6, 1896.
[21] R. Cox: Montreal Medical Journal, August, 1899.
[22] O. Martin: La Presse Médicale, August 27, 1898.
[23] C. L. Lang: Medical Council, April, 1900.
[24] Kerley: Pediatrics, June 1, 1897.

both disorders traceable to suprarenal inadequacy. "The patient developed slowly, both mentally and physically. She did not walk until nearly three years old. She was frail and excitable as a growing child. When six years old she had a severe attack of measles. During the six years that intervened she enjoyed fair health. She made slow progress at school." Not only was there evidence of infantile myxœdema, therefore, but the general vulnerability of the adrenals had been increased by severe measles. That the cellular protoplasm of this child should be correspondingly vulnerable to disturbances, chemical or physical, as a result of the suboxidation to which her organism had been submitted since her birth, seems reasonable. When twelve years old, "a blow on the right side of the neck, from behind, which caused intense fright and hysteria," served as starting-point of the exophthalmic goiter. A feature to be emphasized here is that "the pulse was small and soft": evidence that the adrenals were unable to respond above a certain limit to the excess of thyroidal secretion poured into the circulation, or that the case had promptly lapsed into that of suprarenal insufficiency. Five months' treatment with thyroid yielded a satisfactory result.

Two cases reported by H. L. Winter[25] may also be included in this class. The patients were sisters, 22 and 17 years of age, respectively, of Swiss birth. The former was "stout and anæmic," in the latter there was "no marked anæmia"—evidence that *some* degree of anæmia—pallor—was present. The flushing was not of the continuous kind, but of the kind brought on suddenly, and characterized by the author as "flushes," just as the muscular signs are termed "startings"—sudden expressions of equally sudden contractions or spasm of the central vascular trunks, arising from weak adrenals, as flashes of flame arise from stirred embers. "In Cases I and II" (the cases referred to), says the author, "exception might be taken to the diagnosis. The rapid heart-beat, usually the first symptom of a typical case of exophthalmic goiter, was not present; the pulse was high only during an attack of palpitation." In the light of our views no exception could with

[25] H. L. Winter: *Loc. cit.*

justice be taken to the author's diagnosis. Both cases had weak adrenals, and to this weakness were mainly due the signs witnessed, and it is owing to this, as well as in all cases of a similar kind, that thyroid extract proved efficacious.

To illustrate the solidity of these deductions, the following selection from A. J. Hutchinson's[26] review of an article by Maurice Faure may be adduced: "A woman, aged 32, began to develop symptoms of Graves's disease, and by the end of six years presented a complete picture of exophthalmic goiter. During the seventh year cardiac insufficiency supervened; during the eighth year the signs of exophthalmic goiter retrogressed, and the cardiac condition improved; then during a period of about three years, during which the signs of Graves's disease, especially the tachycardia, still persisted, myxœdema appeared. During these three years the treatment was at times directed against the myxœdema,—viz.: thyroidin or thyroid gland; at others against the cardiac condition,—viz.: digitalis, with suitable diet, etc. During the eleventh year cardiac insufficiency became very serious, the myxœdema increased, and finally the patient died in asystole." . . . "Exophthalmic goiter and myxœdema co-existed in this case during at least two years. It is therefore impossible that the former should be due to increased secretion, while the latter should be due to diminished secretion by the thyroid gland. . . ." A number of cases have been reported by Baldwin, Gowan, L. Gautier, Joffroy and Achard, and others in which myxœdema followed exophthalmic goiter.

That this conception of the pathology of exophthalmic goiter and its close connection with suprarenal functions is able to bear close scrutiny may also be illustrated by the researches of Scholtz.[27] If the first stage of the disease, that of overactivity of the adrenals induced by excessive thyroid secretion, is really characterized by hyperoxidation, rapid tissue-waste must occur, and the products, being oxidized as fast as formed, must also be eliminated as highly oxidized end-products. Scholtz, seven years ago, found that there was in

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[26] A. J. Hutchinson: British Medico-Chirurgical Journal, from La Presse Médicale, Sept. 23, 1899.

[27] Scholtz: Centralblatt für innere Med., Nos. 43 and 44, 1895.

exophthalmic goiter an increased excretion of phosphoric acid in the stools amounting to tenfold the normal, as compared to one of only 25 per cent. in a healthy person. He concluded, therefore, that the thyroid gland has an important influence on the metabolism of phosphoric acid. Experimental evidence also bears this out, since Roos[28] found that, in healthy dogs, feeding with thyroid caused an *increased excretion of nitrogen, sodium chloride,* and *phosphoric acid.* This is further confirmed by the beneficial effects obtained empirically with *sodium phosphate,* which will be referred to when exophthalmic goiter is further analyzed. Again, G. R. Murray[29] refers to a case examined post-mortem by Dr. Auld as follows: "The state of the pituitary and thymus glands had received considerable notice in connection with morbid alterations of the thyroid, but Dr. Auld suggested a more systematic examination of the suprarenal gland. In a case of fully developed exophthalmic goiter in a young woman, aged 25, in whom death occurred from an intercurrent malady, he had had an opportunity of examining this organ. He was much interested to find that the medullary portion of the gland was much *hypertrophied* and the nuclei of many of the glandular cells were undergoing division." That "hypertrophy" is the result of overaction of the glands has, as we have seen, been experimentally demonstrated. Finally, the clinical observations of Breuer[30] may be adduced to show that the active factor in the whole process is iodine. Swiss investigators had already noted that even small doses of iodide of potassium were capable of bringing on mild symptoms of exophthalmic goiter. Breuer witnessed nine cases in which the disease could directly be traced to the administration of iodine.

If we now endeavor to garner the progress so far made in the present inquiry, a prominent feature soon appears: *i.e.,* that we have transferred to the adrenals a long list of symptoms that were thought to be associated with abnormal activity of the thyroid gland. We have done more: the signs referred to are no longer incidental elements of the symptom-complex

[28] Roos: Zeitschrift für physiol. Chemie, Bd. 21.
[29] G. R. Murray: British Medical Journal, Jan. 20, 1896.
[30] Breuer: Wiener klin. Wochenschrift, July 19, 1900.

we term "exophthalmic goiter" or "Graves's disease"; they have been traced as *pathological entities* to their source: the suprarenal glands. In other words, the thyroid gland merely supplies a physiological stimulus to the adrenals that they need to keep up their functions to the proper level. Having ascertained that when this stimulation is excessive certain symptoms appear, we can conclude that, *whenever* they appear, they invariably have the one and same origin: *i.e.*, excessive suprarenal activity.

Again, we have ascertained, by analyzing the *modus operandi* of thyroid extract in the treatment of exophthalmic goiter, that the cases benefited could no longer be considered as examples of suprarenal overstimulation, but, on the contrary, as cases of suprarenal insufficiency totally independent of the thyroid glands. Indeed, it has become evident that some cases of exophthalmic goiter are primarily due to inadequate functional power of the adrenals, the unusual stimulus of even an incipient case of Graves's disease inducing suprarenal insufficiency at a very early stage of the disease. This is doubtless a compensative process which must greatly reduce the number of instances among children, adolescents, and weaklings of all kinds. We are thus normally led to the conclusion that:—

1. What we term exophthalmic goiter is a syndrome ascribable:—

(a) To overactivity of the adrenals, due primarily to excessive thyroidal secretion in the blood; then, in the second stage:—

(b) To insufficiency of the adrenals: i.e., when the excessive thyroid secretion has induced their exhaustion or that of their centers.

2. All symptoms which have heretofore been directly or indirectly ascribed, in this disease, to the thyroid gland should be attributed to excessive or insufficient activity of the adrenals.

Exophthalmic goiter has given us a general idea of the phenomena brought on by suprarenal overactivity, but it affords but a very limited *exposé* of those of insufficiency. We will, therefore, continue our analysis of the relationship between the thyroid and the adrenals through myxœdema and cretinism (infantile myxœdema), the remaining general processes at present ascribed to the thyroid gland.

MYXŒDEMA AND CRETINISM AND INSUFFICIENCY OF THE ADRENALS.

Removal of the thyroid gland, when it is followed by death, gives rise to a characteristic train of symptoms in animals. The latter appear dull and apathetic; muscular incoordination, shivers, precede spastic paralysis; the temperature falls rapidly. The cause of the violent dyspnœa witnessed is now apparent; and a casual remark of Wesley Mills's,[31] that the thyroid gland "plays a special part in connection with oxidation," indicates that we must be treading on the right path when we include the adrenals in the process. While Albertoni and Tizzoni[32] observed that the blood showed less power to fix oxygen, Masoin[33] found that the relative quantity of oxyhæmoglobin in the blood was diminished in proportion as the morbid results of thyroidectomy progressed. We can at least assume, therefore, that the marked emaciation witnessed is due to the imperfect nutrition which impaired oxidation of the organism involves, that the tetanic convulsions point to imperfect oxidation of waste-products, and that insufficiency of the adrenals due to reduced thyroidal activity underlies all the morbid phenomena that follow thyroidectomy.

That imperfect, inadequate, or arrested thyroid secretion can cause myxœdema has been established. In all cases in which the diagnosis was unmistakable, the glandular elements of the thyroid have been found markedly compromised. Adami[34] found the specific cells replaced by fibrous tissues in the majority of cases collected, and in less advanced cases the degenerated remains of vesicular epithelium, along with areas of the latter showing a tendency to compensatory hypertrophy. In no case diagnosed as myxœdema did he find the gland normal or but little affected. In infantile myxœdema—*i.e.*, cretinism—either the thyroid is totally absent or there is more or less deficiency of glandular elements and excess of connective tissue with cellular *débris*. De Coulon[35] found that the colloid

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[31] Wesley Mills: Canadian Practitioner, Oct., 1895.
[32] Albertoni and Tizzoni: Maragliano: Gaz. degli Ospedali, Oct. 20, 1894.
[33] Masoin: Bulletin de l'Académie de Méd. de Belgique, No. 1. p. 88, 1895.
[34] Adami: Trans. Congress of American Physicians and Surgeons, 1897.
[35] De Coulon: Virchow's Archiv, vol. cxlii, p. 53.

substance was absent in the majority of the alveoli. If thyroidectomy can so inhibit the suprarenal functions as to so materially interfere with the oxidation processes as to cause death, such marked structural lesions as these must produce correspondingly great functional disorders also ascribable to impaired oxidation.

The symptomatology of infantile myxœdema upholds this view in every way. The temperature of cretins is invariably subnormal; they always suffer from cold. The nutrition of all tissues is impaired: the brain remains undeveloped, the fontanelles often remaining patent; the first and second dentitions are delayed; the skin is dry and thickened; the hair is thin and coarse, sometimes absent; the nails are short, brittle, and striated. Growth is very slow and arrested at an early age, ossification being tardy and the epiphyses appearing late. The muscular system is weak and the head tends to droop forward, but no spasmodic or epileptoid movements occur. The genital organs show no sign of development, testes and ovaries being infantile. There is a marked tendency to severe hæmorrhage from the uterus, gums, and nose, and cyanosis is often observed. Osler and Norton[36] refer to the investigations of Magnus Levy[37] as follows: "In four cases which he studied he found a diminution in the consumption of oxygen and formation of CO_2, whereas in Graves's disease it has been more than once proved that there is a marked increase in the consumption of oxygen and in the formation of carbon dioxide." Finally, the well-known effects of thyroid extract in these cases in enhancing oxidation may be exemplified by the prevailing views, which the following excerpt, taken from an article by G. N. Crary,[38] correctly shows: "Increased metabolism is shown by (1) elevation of temperature; (2) increased appetite, with more complete absorption of nitrogenous foods; (3) loss of weight, with nitrogen excreted in excess of that taken in the food; (4) growth of skeleton in the very young; (5) marked improvement in the body-nutrition generally." Indeed, every

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[36] Osler and Norton: "Sajous's Analytical Cyclopædia of Practical Medicine," vol. iii, p. 590.

[37] Magnus Levy: Verhandl. des Congr. f. innere Med., Wiesbaden, 1897.

[38] G. N. Crary: St. Louis Med. and Surg. Journal, July, 1895.

abnormal condition present, including the mental torpor, seems to gradually recede, until in many cases the change produced is truly phenomenal, a fact readily understood when we consider that the process enhanced by the thyroid is the one upon which all vital functions depend: *i.e.*, general oxidation.

Myxœdema in the adult affords a picture varying from that of cretinism in that the morbid phenomena are the result of retrograde changes in normal tissues, whereas in infantile myxœdema the cellular structûres have never been brought to their normal nutritional standard. The most striking difference shows itself in the superficial swelling, the result of perverted cutaneous and subcutaneous functions, which functions have not been fairly developed in the cretin. If, for example, the thyroid arsenic found by Gautier *does* play a rôle in this connection, the skin, nails, and hair of the cretin may have never received their normal supply, while those of the myxœdematous subject may have lost theirs through the thyroid disorder. The other signs, however, are very similar: the hypothermia is the same, the tip of the nose, the lips, and the ears being sometimes bluish, and as cold as marble; the pallor of the skin is also observed over all mucous surfaces; the nutrition of all tissues is impaired—witness the mental torpor, the brittle teeth, the tumefied tissues, the lusterless hair, the alopecia, the brittle nails, etc.

The muscular impotence recalls that of the secondary stage of exophthalmic goiter even to the paresis of the orbicularis; the lids droop over the eyeball, and, if exophthalmos does not occur, it is because the orbital vessels have not been submitted to the centrifugal pressure of the first stage. The copious lacrymation and nasal secretion is also observed in the cretin. The patient is capable of spurts of strength, however, as shown by Charcot: an index that vital functions are only in abeyance and that we are not dealing with structural changes. The muscular exhaustion further shows itself by the inability of the patient to stand normally, the quivering of weakness, the ataxic gait observed at times (Hammond), and the oft-noticed fibrillary tremor, ending in some cases with paralysis. But again must we note the absence of tetany, that condition brought about through accumulation of physiological

waste-products, which products, in myxœdema, the unstimulated adrenals can just about destroy through what oxidation they are able to induce. Indeed, this is the key to the differential results observed in thyroidectomized animals especially as between the carnivorus and herbivorous. Nature again provides protection against this source of danger, since myxœdematous subjects dislike meat (Pel). That tissue-metabolism is markedly reduced in myxœdema is shown by the decrease of urea and uric acid in the urine; but, given an animal suddenly deprived of its thyroid, the equally sudden interruption of adequate adrenal function involves arrested destruction of what toxic products are already in the system, xanthin bases especially. A second cause for suprarenal insufficiency is thus created which correspondingly reduces oxidation, with all its nefarious results. Here, however, an important factor comes into play: the avidity of the tissues for oxygen.

The oxygen-carrying corpuscular elements are not only depleted of their oxygen by them, but that available for antitoxic purposes in the serum is also taken up. Obviously accumulation in the latter of *unoxidized* toxic products of cellular and food metabolism must occur. As a result, practically all the energy which the remaining suprarenal activity affords through the oxygen it supplies the organism, is concentrated in the organic cellular elements, while the blood-stream teems with toxic products.

We can now understand why various investigators, as previously stated, found that the blood of an animal deprived of its adrenals and which is beginning to show toxic symptoms has such poisonous effects when injected into another animal from which the adrenals have been removed shortly before. It is to this difference between the comparatively immune tissues and the highly toxic blood that the tetanus and epileptic convulsions witnessed seem to be due, since the latter are, after all, but intense manifestations of activity, caused, judging from the action of toxic drugs, by large doses of physiologically-produced toxics. Yet, why the paroxysmal feature of these manifestations? We have seen that in the type of exophthalmic goiter attended with congenital or acquired suprarenal inadequacy there occur what Dr. Winter called "flushings" and

"startings." These represent the subacute phenomena of which suprarenal spurts of activity are the source and of which tetanus, epilepsy, rabies, and kindred disorders are the acute expressions.

Disorders of sensation become normal results when we consider that the total loss of tone of the central vascular trunks practically depletes the peripheral tissues of their blood and that what blood does reach them is poor in oxygen. Sensation is blunted especially where, as is the case with touch, it is usually most delicate. When under the influence of thyroid extract the tumefaction disappears, the sensibility returns, proving that the nervous and cutaneous structures were not structurally impaired, but merely inactive through the absence of their *pabulum vitæ*. Perversions of the senses of smell and taste, mental apathy, hallucinations, melancholia, vertigo, marked reduction of the flow of urine, albuminuria, and glycosuria are also witnessed. Death occurs from exhaustion when, as in exophthalmic goiter, an intercurrent acute disorder does not, as is usually the case, carry the patient away before this stage is reached.

To emphasize the remarkable effects of thyroid extract in myxœdema and cretinism is unnecessary. All the symptoms enumerated sometimes disappear, and it is evident that this wonderful result is obtained through enhanced oxidation in all parts of the organism, and procured through the suprarenal overactivity induced.

Proof of all this is afforded by the fact that it is not only in diseases in which the entire vital mechanism is held in check by the absence of thyroid secretion that the effects of the extract prevail. They are the same whenever, as in most cases of myxœdema benefited by it, organic lesions of the adrenals themselves or of any other vital structure are not present to totally prevent the continuation of life. Probably the nearest condition to uncomplicated myxœdema—*i.e.*, a condition in which the human machine is simply in a state of vital abeyance—is catalepsy. In this disorder thyroid extract should also prove efficacious if oxidation through induced activity of the adrenals is the key to the process involved. The experience of R. Hessler, of the Northern Indiana Hospital

for the Insane,[39] may be adduced to show that it is as active here as in myxœdema:—

"The case was that of a cataleptic who had lain immovable in bed for over three years; there was an absence of motor and sensory activities; the feeding was by means of the nose-tube. Under increasing doses of gland constantly increasing activities resulted, until finally the patient 'returned to life' and was able to speak and walk. At a time when 75 grains were given daily, symptoms of exophthalmic goiter appeared, and the remedy had to be discontinued temporarily, the pulse going up to 160. In the course of a few days the patient relapsed to his usual condition, but 'revived' on again receiving the remedy, with a return of the symptoms mentioned. A similar case recovered promptly in a few weeks on small doses."

It thus seems conclusively shown that, to the long list of symptoms ascribed to the suprarenal glands, as represented by the first stage of exophthalmic goiter, we can now add another equally long list of phenomena: *i.e.*, those represented by myxœdema and infantile myxœdema, but due to suprarenal insufficiency instead of overactivity. It also appears that, as is the case with the signs of the latter, those observed in both forms of myxœdema, whenever they occur, are also invariably traceable to insufficiency of the adrenals. We have also established the connection between myxœdema and the second stage of exophthalmic goiter, and realized that thyroid extract is efficient in this stage of the disease because of the latter's identity as myxœdema in some cases and as simple suprarenal insufficiency in others, the thyroid gland in the latter case remaining active and therefore obviating the cutaneous symptoms, through, perhaps, the arsenic it furnishes these structures. On the whole, it thus becomes apparent that:—

1. Myxœdema and infantile myxœdema (cretinism) are due to insufficiency of the adrenals, the result, in turn, of absence or diminution of the secretion supplied to the blood by the thyroid gland.

2. All individual symptoms witnessed in the course of these diseases should be ascribed to reduced activity of the adrenals.

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[39] R. Hessler: Jour. Amer. Med. Assoc., and Dublin Jour. of Med. Science, March, 1897.

THE THYMUS GLAND AND THE ADRENALS.

If the conclusions just recorded as to the relationship between the thyroid gland and the adrenals are sound, there is considerable analogy between the effects of thymus on the organism and those of the thyroid. Svehla's[40] well-known experiments add further evidence to that submitted to the effect that the thyroid gland only assumes its functions at birth, extract of fœtal thyroid having proven inert, while extract obtained from the thyroids of infants during the first month of life was effective. Precisely in the same manner did thymus extract behave: fœtal-thymus extract produced no effect, while that obtained from the thymus glands of infants in the first month caused increase in the frequency of the pulse and lessened blood-pressure. Further proof of the solidity of the views herein advanced is also shown by his conclusions —based on experimental evidence—that "among children of the same age the thymus extract is the strongest; less so the thyroid; and still less the adrenal. In adults, however, the adrenal outstrips both other glands." The influence of this suprarenal inadequacy is an important factor, we have seen, in the predilection of children for infectious diseases.

Svehla refers to "increased frequency of the pulse and lessened blood-pressure" as the prominent effects of thymus extract: evidence, if its action corresponds to that of thyroid, that a toxic dose had been administered to the experimental animal. This is confirmed by the fact that other typical symptoms were present: *i.e.*, muscular weakness, dyspnœa, and general collapse,—a condition from which the animals could be saved by the timely administration of thymus extract, which promptly restored the normal vascular pressure. The similarity between the physiological actions of thyroid and thymus as suprarenal stimulants is further shown by the experiments of Isaac Ott[41] in rabbits. In these animals powdered thymus caused the pulse to increase its rate and the blood-pressure momentarily to *rise*, but soon to *fall* considerably: a suggestive sequence of events. In another animal he found that the thymus caused the respiration to increase and that section of the

[40] Svehla: Archiv für exper. Pathologie, Bd. xliii.
[41] Isaac Ott: Medical Bulletin, May, 1898.

vagi did not alter the result. In a third case he noted that the "thymus caused a slight increase of temperature, but that the increment was not beyond the normal variant." That the action is not antagonistic to the action of the thyroid secretion, as thought by some observers, can easily be shown. If such were the case Svehla could not have caused temporary recovery of his *collapsed* animals; nor would Cunningham[42] have found it as efficacious after removal of the thyroid gland as thyroid extract itself, nor would Ott have found the "rise" to precede the "fall."

Thymus extract seems to prove efficacious in precisely the same class of cases of exophthalmic goiter as thyroid extract. Owen,[43] for example, recalled his successful result in a marked case of twenty years' standing, but he indirectly points to his patient's advanced condition by the statement "the next three months he spent mostly in bed." His second case complained of feeling "low and weak," sweated profusely, became bald, and had tremors and pigmentation. A third case benefited was one in which breathlessness, general weakness, and emotional outbreaks prevailed. He also refers to an extremely aggravated case treated successfully by Maude,[44] in which drugs, including belladonna, had proven ineffectual. Under thymus tabloids, 45 grains daily, the patient rapidly improved, and invariably relapsed when they were discontinued. Maude having observed that the tremors were particularly relieved by this form of treatment, Owen tried fresh thymus in paralysis agitans,—which, as shown, is a sign of the advanced stage, that of suprarenal insufficiency,—"with the result that the tremors were unmistakably benefited and the mental state and the muscular condition greatly improved."

An analytical study of Maude's cases shows that they are all of the advanced type. In the first "the heart and paralytic conditions were such as to confine her to bed for over a year." The second "belonged to a highly neurotic family; goiter had existed since childhood," and the "tremor, excessive muscular weakness, and cardiac disturbance were all well marked." The

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[42] Cunningham: Jour. of Experimental Medicine, p. 225, vol., 1898.
[43] Owen: British Medical Journal, Oct. 10, 1896.
[44] Maude: Lancet, July 18, 1896.

third had recovered from a previous attack without thymus; hence its use after recurrence as the result of grief cannot serve as fair example. The fourth was of thirty-two years' standing, and the patient had suffered from "various severe nervous symptoms," viz.: paralysis of various basal nerves, ophthalmoplegia, paralysis of facial, ambulatory epilepsy, etc." . . . "She had had, in 1894, twenty-four motions in one day of almost pure arterial blood. In November, 1895, she had a sudden profuse hæmatemesis, followed by collapse so extreme that she seemed moribund. After she rallied she was given 45 grains of thymus tabloids per day, for a month, and her improvement was very remarkable; she remained in a fair state of health for many *months*." Degeneration of the arterial walls probably existed in this case, and it seems likely that the loss of blood can be credited with the relief afforded. Todd's case[45] had an epileptic mother, her sister had suffered from *myxœdema* and had been cured with thyroid extract, and she was herself a "very delicate" girl. N. J. McKie's case[46] and those of R. T. Edes[47] and Philip James[48] also represent instances in which there were debilitated adrenals. In a case successfully treated by Boisvert[49] the presence of melancholia also shows that weakened adrenals were present and that the increased insufficiency of these organs brought on by the thymus, as was the case with two of the patients referred to by Dr. Winter in which thyroid extract was used, led to recovery. These examples, which could be multiplied, not only indicate that thymus extractives are active when there is impaired functional activity of the adrenals, but they also tend to prove that the thymus gland is very similar to the thyroid in its action upon these organs.

The harmful effects of thymus in the first stage are illustrated by a case described by Watson Williams,[50] who found that it aggravated the tachycardia and pyrexia: evidence that it had been given while suprarenal overactivity was present.

[45] Todd: British Medical Journal, July 25, 1896.
[46] N. J. McKie: British Medical Journal, March 14, 1896.
[47] R. T. Edes: Boston Med. and Surg. Journal, Jan. 23, 1896.
[48] Philip James: Australasian Med. Gazette, July 20, 1897.
[49] Boisvert: Revue Médicale de Montréal, June 21, 1899.
[50] Watson Williams: Clinical Journal, Dec. 11, 1895.

In the large proportion of cases reported, however, there is no marked untoward effect produced. It seems to be much less active in this connection than the thyroid extractives. In fact, in some cases—probably those on the border-line of suprarenal insufficiency—it appears to act as a nutrient tonic, as noted by Hector Mackenzie[51] after a study of twenty cases in which he had tried thymus gland, and to which further reference is made below.

The connection between the thymus and the adrenals is also illustrated by the experiments of Abelous and Billard,[52] in which removal of the former gave rise to symptoms similar to those that follow adrenalectomy: even to discoloration of the skin, great muscular weakness—lapsing into paralysis, blood-changes, œdema, etc. They also found that the secretions of the experimental animals were markedly toxic: evidence of inadequate oxidation. On the whole, this evidence, considered collectively, seems to indicate that *the thymus gland supplies some substance which directly or indirectly stimulates the secretory functions of the adrenals, and thereby enhances the activity of the oxidation processes.*

What is the nature of the agency through which the thymus stimulates the adrenals, and what is the specific relationship between these organs? These questions are suggested by the fact that, while undue activity of the thymus increases that of the adrenals, there seems to be no evidence that the thymus can alone—*i.e.*, independently of the thyroid—give rise to either exophthalmic goiter or myxœdema. In all cases of the former disease ascribed to the thymus found in available literature there is invariably thyroidal involvement. Yet the thymus seems sufficiently active to bring the adrenals to their normal activity when the general vital processes are depressed. We have seen, on the other hand, that its removal gives rise to symptoms recalling those of adrenalectomy.

Baumann[53] found minute quantities of iodine in the thymus also; but other experimenters have failed to find even this trace, and have ascribed Baumann's findings to contamina-

[51] Hector Mackenzie: American Journal of the Medical Sciences, April, 1897.
[52] Abelous and Billard: Archives de Physiologie, Oct., 1896.
[53] Baumann: Münchener med. Wochenschrift, p. 311, 1896.

tion from neighboring thyroidal tissues. Even granting that such a trace of iodine exists, we are well aware that the thyroid does not owe its power to stimulate the adrenals to "a trace"; the labors of many investigators have conclusively shown that it must supply the organism with a considerable amount of this substance. Evidently we must look elsewhere for the solution of this problem, and, data bearing directly upon the subject being wanting, we shall have to seek for the required substance through its comparative behavior in the organism, and the manner in which its effects vary in the latter from those of thyroid extractives.

Valuable in this connection are the autopsies of 61 children at the Hôpital des Enfants-Malades, of Paris, performed by Albert Katz at the request of Bourneville.[54] All these children had died of various diseases, their ages varying from one month to thirteen years, though 41 were under two years of age. In *all* of the 61 bodies the thymus gland was *present*, while in 28 mentally weak and epileptic children examined by Bourneville the thymus was *absent in 25*. In another series of 292 cases it was absent in 74 per cent. But these comprise not only all varieties of mentally abnormal children, but also various degrees of imbecility; so that the remaining 26 per cent. may have included a number of instances in which mental development was high as compared to that of the cases in which the organ was absent. Yet, to avoid favoring our own line of argument, we will consider that in three-fourths of imbecile children, some of which were epileptics, the thymus gland was absent.

These observations become elucidative when analyzed through the effects of thyroid extract. Especially suggestive is the following casual remark of Cabot's, in the course of a valuable paper published some years ago[55]: "The fact that in myxœdematous children and cretins the thyroid treatment is associated with notable growth in height has led some observers to try its effects in dwarfed children not myxœdematous, to see if their development could not be helped. I have collected 10 such cases, 3 in idiotic children and 6 in whom the lack of

[54] Katz: Le Progrès Médical, June 23, 1900.
[55] Cabot: Medical News, Sept. 12, 1896.

development was mainly physical. A considerable increase in height was observed in all the cases, *but the mental symptoms were not improved.*"[56] It seems evident that if, on the one hand, the vast majority of cases of mentally weak children do not possess thymus glands, and that, on the other, thyroid extract will enhance growth of idiotic children (not myxœdematous ones, *i.e.*, cretins), the oxidation processes, stimulated by the thyroid through its action on the adrenals, are inadequate to alone bring on improvement of the mental symptoms. Again, it becomes evident that it is upon the thymus that the mental development depends, and, finally, that it is to some agent which the thyroid gland does not contain that this development is due.

This enables us to eliminate iodine as the main active principle of the thymus gland, and, our inquiry being disconnected from the oxidation process through the evident inefficiency of the thyroid to restore mental functions, we are led to seek for a chemical body that will enhance cerebral nutrition. Can we expect such an hypothetical agency, however, to concentrate its effects upon the brain alone? This is hardly probable, judging from analogy, and the nervous system at large must also utilize it physiologically. Our field is therefore broadened, since an agency connected with the nutrition of the brain alone, or one playing the same rôle in respect to the entire nervous system, may serve our needs. This is, to say the least, fortunate, for the chemistry of brain- and nerve- matter is far from well known, and even a good analysis—*i.e.*, one based upon the more salient data available—would be impossible were the limits of the inquiry at all narrowed.

Of the solid constituents of nerve- and brain- matter, three stand out prominently: cholesterin, cerebrin, and lecithin. Cholesterin, considered by Austin Flint, Jr., as a waste-product of cerebral and nervous origin, though it represents one-half of all the solids, shows no molecular constituent capable of assisting us ($C_{26}H_{44}O$), the fact that the thyroid secretes a specific agency being taken as standard; nor does cerebrin ($C_{17}H_{33}NO_3$), though both this and the preceding body are found in abundance in the cerebro-spinal axis and nerves.

[56] The italics are our own.

With lecithin, sometimes termed "phosphorized fat," which represents about one-tenth of the solids, the case is different, since its formula ($C_{44}H_{90}NPO_9$) suggests that phosphorus may represent the constituent we are seeking. It is not only a prominent component of the whole cerebro-spinal and nervous systems, however, but it is also a constituent of the red and white corpuscles, milk, bile, serum, semen, and pus. Another body, protagon ($C_{160}H_{308}N_5PO_{35}$), has also been isolated from brain-substance by Liebreich, who considered it as the main cerebral constituent: an opinion sustained by Gamgee and Blankenhorn.[57] Hoppe-Seyler and other investigators are, however, inclined to consider it as a mixture of lecithin and cerebrin. Whether this be the case or not, phosphorus again appears as the only element capable of being at all associated with the question in point.

To merely adopt phosphorus as the characteristic constituent of the thymus gland, however, and declare that it is through its *minus* or *plus* production that the mental attributes of children are developed, would merely constitute a theory. As a stronger position is desired for all the deductions vouchsafed in this work, collateral evidence must be sought.

The observations of Cabot, that, while thyroid extract stimulates growth, it fails to enhance mental development in idiots other than myxœdematous ones, raises the question as to whether such results can be due to the absence of phosphorus in the thyroid. If such is the case, the absence of this element should also show itself in the results obtained from the extract in some other disease, if any structure other than the brain and nervous system, in which a morbid deficiency of phosphorus also exists, is a feature of that disease. We know, for example, that phosphorus is introduced into the organism with food, and that calcium phosphate, by becoming deposited in the bones, gives them their hardness. Is there any evidence that the bones of subjects in which thyroid extract is successfully administered lack of this hardening constituent? Referring to the use of thyroid extract in cretinism, T. Telford-Smith[58] makes the following statement: "I have

[57] Gamgee and Blankenhorn: Journal of Physiology, vol. ii, 1879.
[58] T. Telford-Smith: Lancet, Oct. 2, 1897.

found that during thyroid treatment the rapid growth of the skeleton leads to a softened condition of the bones, resulting in a yielding and bending of those which have to bear weight; and, as cretins under treatment become more active and inclined to run about, this tendency to bending has to be guarded against." After referring to the experiments of Hoffmeister in rabbits and those of Eisenburg in sheep and goats in which bending of the legs was caused by removal of the thyroid, he adds: "While in rickets, however produced, there is perverted and delayed ossification resulting in softening and bending of the bones, under thyroid treatment in cretinism there is rapid resumption of growth in the skeleton, leading to softening, which is most marked in the long bones and at the epiphyses." That we are dealing here with an absence of phosphorus and that the calcium phosphate serves to harden the bones concurrently with their growth seem obvious.

But why does this not occur in all cases? Simply through the fact, ascertained by Marie,[59] that the thymus is almost always persistent in cases of cretinism. When thyroid extract is administered, therefore, the increased oxidation procured by stimulating the adrenals also enhances thymic activity, and the assimilation of phosphorus is increased in proportion. This is proven by the experiments in animals by Hoffmeister and Eisenburg, referred to by Telford-Smith. If removal of the thyroid caused bone-softening in these, it is because—in the light of our conception of the process—the adrenals were rendered inadequate, and, oxidation being impaired in proportion, the thymus also failed functionally.

This process, however, involves the need, in the structures of the thymus gland, of a metabolic process culminating in the production of an internal secretion laden with phosphorus-containing bodies. Quotations from a study of the nucleins and nucleoproteids in their relation to internal secretion by Chittenden[60] will serve to enlighten us: "The manufacture of the specific substances which give character to the various internal secretions is obviously a function either of special

[59] Marie: Bulletin et Mémoires de la Société Médicale des Hôpitaux de Paris, p. 136, 1893.

[60] Chittenden: Boston Med. and Surg. Journal, August 20, 1896.

cells contained in the gland or it may be in some cases an inherent quality of all the cellular elements of a given gland. In the pancreas the formation of the active agent is apparently limited to an interstitial, epithelium-like tissue occurring in isolated patches throughout the gland and especially characterized by its vascularity. This epithelioid tissue is certainly distinct from the secreting alveoli, and is suspected, at least, of being the source of the internal secretion. Again, in the suprarenals, as Schäfer and Oliver have shown, the active principle, which has such a marked influence upon the heart and arteries, is contained only in the medulla of the gland, and not in the cortex, the medulla forming about one-fourth of the gland by weight." . . . "If we take the content of phosphorus as a measure of the proportion of nucleic acid contained in the various forms of nucleoproteids thus far studied, we find exceedingly great variations in the amount of this acid present in the molecule: a fact which may be taken as evidence of the large number of molecular combinations present in the protoplasm of different cells. Thus, from the kidneys we obtain a nucleoproteid with only 0.37 per cent. of phosphorus, while, as representing *the other extreme*,[61] we have in the pancreas a nucleoproteid containing 4.71 per cent. of phosphorus and *in the lymphoid cells of the thymus a corresponding body with 3.5 per cent. of phosphorus.* . . . The very nature of the many bases which come from the cleavage of the nucleic acids outside the body; the ready convertibility of these bases into other allied bodies *by oxidation and reduction;* their own physiological action, which, though mild, is marked; the possibility—nay, the probability—that many other catabolic products may be obtained from these nucleic acids; and, further, that still other nucleic acids at present undiscovered may exist in the cell-protoplasm, all offer good reasons for believing that the nucleins and nucleoproteids, which are the most prominent constituents of the protoplasm of all cells, are the most probable antecedents of the internal secretions."

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[61] All the italics are our own.

There is evidently a sound foundation for the belief that phosphorus is the active constituent of the thymus gland. If thyroid extract failed to improve the mental condition of the ten cases collected by Cabot notwithstanding the increased growth witnessed, it is either because the thymic gland in all was structurally unable to respond to the increased oxidation which the stimulated adrenals induced or because no thymus gland was present. That this gland is absent in the vast majority of weak-minded, but not myxœdematous, children is shown by the researches of Bourneville and Katz. That phosphorus is the main specific constituent of brain- and nerve-substance is a recognized fact, fully sustained by physiochemical data. That thyroid extract does not improve non-myxœdematous idiocy or weak-mindedness in children owing to the absence of phosphorus in the organism is shown by the corresponding effects it has on the skeleton of some cretins, as observed by Telford-Smith, the bones, by their softness, showing the absence of the hardening that calcium phosphate procures. Finally, that the adrenals, through the normal oxidation processes insured by them when adequately stimulated by the thyroid secretion, sustain the activity of the thymus up to its proper standard is shown by the experiments of Hoffmeister and Eisenburg, in which removal of the thyroid of various—herbivorous—animals caused bending of the legs. The thyroid is thus able to stimulate the adrenals, and the adrenals in turn can stimulate the thymus. But does the thymus *physiologically* stimulate the adrenals?

The fact that the thymus gland is but a temporary structure, one calculated to atrophy when its functions as a building organ are accomplished, would seem to suggest that stimulation of the adrenals is not one of these functions. If the deductions herein submitted are sound, it would appear to stand prominently as a bone-forming organ and general phosphorus-purveying organ from the time of the completion of its lymphadenoid elements during intra-uterine life until the final elaboration of the skeletal frame-work,—*i.e.*, around the period of puberty,—its powers gradually receding as permanent organs are developed. This conception of its purpose does not appear to have suggested itself to anyone so far, but it is quite

in keeping with the collateral observations of a number of the best of modern embryologists.

The most prolific source of leucocytosis, as is well known, is the bone-marrow. In the process of bone-formation during fœtal life, the first points of ossification appear during the second month, but it is only during the fourth that the development becomes markedly active on all sides. That the most active work of the thymus is performed during intra-uterine life is well known; this, therefore, coincides with its most active bone-forming period. It seems reasonable to conclude that so important a function as leucocytogenesis should not devolve upon structures undergoing formation, and also that the bone-forming organ should be intrusted with the function which ultimately would constitute the main active attribute of their product. Bone-marrow being the main leucocyte-forming structure, we should therefore expect the thymus to assume this rôle until the bone-marrow had reached its normal physiological development.

Kölliker has always maintained that the formation of leucocytes was a function of the thymus: a position in which he has been sustained by Prenaut and Oscar Schultze. J. Beard[62] more recently took up the question and studied it with considerable care in the *Raia batis*, the smooth skate. He ascertained that the absence of leucocytes in the earliest period of embryonic blood in vertebrates persists until the first ones are formed within the thymus epithelium and from its epithelial cells. In embryos from twenty-eight to forty-two millimeters long the formation and emigration of leucocytes from the thymus becomes very active, and at this time there is no part of the embryo, including the blood, that is not infiltrated with leucocytes. This happens before lymphoid structures are developed elsewhere within the body of the smooth skate. Beard believes, with Kölliker, that the formation of leucocytes is a function of the thymus gland; and "the first leucocytes arise in the thymus from its epithelial cells; thus it is the parent-source of all the leucocytes of the body": a conclusion which is further sustained by what appears to us to be a war-

[62] J. Beard: Lancet, Jan. 21, 1899.

ranted deduction: *i.e., that the thymus is the main organ upon which the osseous, cerebro-spinal, and nervous systems depend for their phosphorus during their development.*

We have also seen that leucocytes are included among the bodies that contain phosphorus. The identity of the thyroid as a bone-forming organ is apparently contradicted by Svehla's observation that fœtal thymus proves inert experimentally; but when we recall the fact that it only assumes its function the fourth month, that its inordinate activity may cause it to fix but little of the element itself, there is ample room for doubt as to the value of the experiments. If these facts do not prevail, then all the data submitted, the recognized intra-uterine supremacy of the thymus over other glands, Chittenden's analysis, and several physiologically established facts would also have to be considered wrong.

If the temporary rôle of the organism of the thymus precludes a physiological connection between it and the adrenals, how are the beneficial effects in exophthalmic goiter, to which reference has been made, produced? If the cases analyzed by Hector Mackenzie[63] are studied with a view to ascertain which of the various remedies used by him, including thymus gland and extract, have proven of greatest value, it soon becomes evident that the thymus does not differ much from belladonna, phosphate of sodium, and other agents tried by him. In Case XVIII, for instance, thymus and tincture of belladonna proved beneficial; on the remedies being changed to belladonna and bromide considerable improvement occurred. In Case XXIII all the symptoms except the rapid cardiac action greatly diminished under belladonna and phosphate of sodium. A relapse occurring, the treatment was changed to thymus extract, which also caused decided improvement. Case XXVIII was given belladonna, potassium bromide, and thymus extract, also with excellent results. Case XXX was also given sodium phosphate and belladonna for the first fortnight, which caused the patient to feel "better each time." He was then ordered, in addition to the sodium phosphate, some thymus extract. This caused him to feel "better generally." Case XXIII was evidently one

[63] Hector Mackenzie: *Loc. cit.*

which had already reached the border-line of suprarenal insufficiency; the patient, after having "wasted almost to a skeleton," had more than made up for what she had lost; thyroid and thymus combined proved beneficial. Case XXIV was still further advanced, since "she had no strength or energy" and a good deal of pigmentation about the face; took an alkaline tonic, thymus with thyroid, belladonna, potassium, and grew "weaker and more nervous"; but extract of thymus alone caused her "general condition" to become "better." On the whole, it is plain that thymus acts like any other more or less useful drug, as "a remedy of some value," using Dr. Mackenzie's words, "improving the general condition," and which "in this way may assist toward the recovery of the patient." This confirms the absence of physiological relationship with the adrenals, and tends to show that the *benefit obtained from the therapeutic use of thymus gland is mainly due to the phosphorus it contains.*

This does not mean, however, that it may not prove an exceedingly valuable therapeutic agent in properly-selected cases. In fact, it seems possible that, in the very cases treated with thyroid extract referred to by Cabot, the addition of thymus might have caused the improvement in the mental condition which thyroid alone failed to procure. The absence of the thymus in Bourneville's cases supplies a firm foundation for this thought. Though some benefit has been obtained from sodium phosphate, it seems reasonable to believe that in physiological combination, as it occurs in thymus, phosphorus will prove far more efficacious. Whether it enhances suprarenal activity through this element, or, as does thyroid, through a specific physiological body intended for this special purpose, matters little. It also stimulates the adrenals, and if we do not lose sight of the fact that the *entire cerebro-spinal axis and the nervous system* utilize phosphorus as an all-important specific source of energy, and associate with this the enhanced oxidation which its stimulation of the adrenals procures, we cannot but realize that its intelligent use may insure results unattainable through any other agency. The benefit obtained by Owen in a case of paralysis agitans shows that these are not vain words. Indeed, we must not overlook the fact that im-

paired suprarenal activity reduces the nutritional standard of *all* structures and that all cells fail to appropriate through the reduced metabolism involved their physiological constituents. While, therefore, paralysis agitans should not be classed as a nervous disease, it is nevertheless true that the nervous system, if the adrenals underlie the whole trouble, also suffers from impaired nutrition, and that phosphorus, its source of intrinsic energy, is as necessary to it as oxygen itself.

The purpose of this chapter being to ascertain, as we did in the case of the thyroid, whether any special symptom or disorder could be traced to the adrenals through the mediation of the thymus, we will now summarize the results attained in this connection:—

The testimony adduced seems to show that the stimulation of the adrenals by the thymus is purely incidental, and due to the phosphorus the latter contains in organic combination. Yet experimental evidence demonstrates that the withdrawal of this stimulation and deprivation of phosphorus to which the adrenals are thus subjected can induce suprarenal insufficiency, while, on the other hand, its therapeutic and experimental administration has shown that thymus is able not only to restore the activity of insufficient adrenals, but also to induce overactivity of these organs. A normal deduction suggested by these phenomena is that they are interdependent as long as the activity of the thymus lasts,—*i.e.*, until puberty,—and that *insufficiency of either the adrenals or the thymus during the development of the organism gives rise to morbid phenomena in which both oxidation and the nutritional processes that depend upon bodies containing phosphorus in organic combination are the leading pathogenic factors.* Insufficiency of the thymus by correspondingly reducing the supply of phosphorus to the nerve-centers of the adrenals impairs the activity of both, while the deficient oxidation of the cellular elements of the thymus further inhibits their function. This vicious circle may also prevail in the opposite direction: *i.e.*, in connection with overactivity of either organ.

We thus have again constituted two general classes of pathogenic factors, *i.e.*, overactivity and insufficiency of both organs, which, if examined into in respect to their far-reaching

influence during the process of physical development, are fully as important as those in which the thyroid plays an active part. Indeed, while the thyroid gland physiologically stimulates the adrenals through its iodine constituent and perhaps supplies the cutaneous tissues with their main inorganic body, —*i.e.*, arsenic,—the thymus incidentally stimulates the suprarenal glands, and supplies the bones, the brain, the cord, the nerves, and other structures with their main inorganic constituent, phosphorus. The conclusion seems warranted, therefore, that:—

Impairment of the functions of the thymus and of the adrenals underlies the disorders of nutrition which inhibit the development of the cerebro-spinal, nervous, and osseous systems, during infancy, childhood, and early adolescence.

CHAPTER V.

THE ANTERIOR PITUITARY BODY, THE THYROID GLAND, AND THE ADRENALS AS PARTS OF AN AUTONOMOUS SYSTEM.

In his valuable essay on "Acromegaly" Guy Hinsdale[1] refers to Gauthier's[2] view, that the symptoms of this disease could be divided into two stages, as follows: "Two stages in the course of acromegaly have been differentiated, viz.: the erethic stage and the cachectic stage. The phenomena of *erethism*[3] which characterize the *first stage* embraces, first, a painful hyperæsthesia, which manifests itself in headaches and rheumatic pains; second, an hypertrophy of the muscular fibers, which may give to patients a muscular power greater than usual; third, palpitation of the heart accompanying the hypertrophy of that organ; and, finally, the polyphagia and polyuria, which may be considered to be connected with an erethic state of the respective organs. The *second stage* is characterized by a *cachexia* or a period of decadence. The stage of increase has abated and the phenomena of erethism have disappeared. Muscular atrophy and cardiac dilation and a consequent enfeeblement of the circulation render the patient quite helpless. It is in this stage that bleeding from the nose may ensue, and progressive debility marks the period of decline, which ends in syncope. Epistaxis may also occur early."

It is perhaps unnecessary to point out that all these symptoms recall those of exophthalmic goiter, barring certain characteristics of the latter disease. We have seen, however, that exophthalmic goiter was, in reality, the direct result of suprarenal overactivity, though initiated through thyroid overactivity. The foregoing acromegalic symptoms, therefore, must

[1] Guy Hinsdale: "Acromegaly"; Boyleston Prize Essay of Harvard University, 1898.

[2] Gauthier: Progrès Médical, May 24, 1890, and Jan. 1, 1892.

[3] All italics are our own.

also originate from the adrenals, with some disordered function of the pituitary gland as primary factor. That the latter organ is associated with the characteristic symptoms of acromegaly—*i.e.*, those *not* observed in exophthalmic goiter—is practically established; we have seen that the thyroid gland also gives rise, probably through its arsenic, to special cutaneous symptoms. Our first line of inquiry, therefore, should enable us to ascertain whether the pituitary is also, as are the thyroid and thymus glands, connected functionally with the adrenals.

Vassale and Sacchi[4] found, in 1892, that complete destruction of the pituitary gland in dogs and cats had fatal consequences within two weeks. The symptoms that followed removal were rigidity of the gait, fibrillary muscular contractions and spasms, anorexia, depression, and lowering of the temperature. In more recent experiments they ascertained that all these phenomena, including the hypothermia, could be relieved by an injection of extract prepared from bovine pituitary. In one of the animals experimented upon the symptoms, after lasting for some weeks, gradually disappeared. It was then killed and the fact revealed that the gland had only been incompletely destroyed. Arnoldo Caselli[5] has also found that complete abolition of the functional activity of the pituitary in dogs and cats caused, in the first instance, slowing of the respiration and acceleration of the pulse, then mental depression and disturbances of movements. The latter were characterized by arching of the back and spastic gait, without tonic or clonic contractions of the limbs. Progressive cachexia then appeared, the animal dying comatose. These results have been indirectly sustained by those of other observers. Oliver and Schäfer, for example, found that extract of pituitary caused a marked rise of blood-pressure, with increased force of the heart-beat: an action which they compared to that of suprarenal extract, but with the difference that no slowing of the heart-beat occurred. Szymonowicz reached the opposite result: He found that injections of pituitary extract produced in dogs a slight fall of

[4] Vassale and Sacchi: Rivista Sperimentale de Freniatria, p. 83, 1894.

[5] Arnoldo Caselli: "Studii anatomici e sperimentali sulla Fisiopatologia della Glandola pituitaria," 1900.

blood-pressure, while simultaneously quickening the heart-beat. Howell[6] then ascertained that extracts of the infundibular portion alone of the pituitary body gave rise to a pronounced slowing of the heart, but with an increase of blood-pressure. The latter rose more slowly than it did when suprarenal extract was used, and sank gradually. Repeated injections caused the effects to become less marked or to fail altogether, especially when administered in rapid succession: *i.e.*, before a preceding injection had lost its effect (half an hour or more). The organs affected appeared to have become temporarily immune to the effects of the extract. De Cyon[7] also noted that slowing of the pulse accompanied the rise of blood-pressure. Isaac Ott[8] even obtained this elevation of the arterial tension in rabbits after severing the cord between the atlas and occiput. Hinsdale[9] witnessed a rise of 11 millimeters Hg above normal (90 millimeters), followed by a decline of 13 below normal, also in the rabbit. In a dog, it caused no immediate change of pressure injected intravenously, but at the end of an hour there had been a gradual fall of 10 millimeters.

E. A. Schäfer and Swale Vincent[10] found at least two active substances, in extracts used by them, having distinct physiological actions. From the one they obtained "a simple rise of blood-pressure caused by contraction of the arterioles": a fact ascertained by them "in the splanchnic area" and "not very dissimilar to that caused by extract of medulla of suprarenal." This pressure-raising substance is not soluble in alcohol. The second substance produced "a well-marked fall in arterial pressure, the effect being almost identical in its characters with that caused by cholin."[11] The marked fall of pressure could be obtained repeatedly at short intervals, thus dif-

[6] Howell: Journal of Experimental Medicine, vol. iii, No. 2, 1898.

[7] De Cyon: Archives de Physiologie, July, 1898.

[8] Isaac Ott: Medical Bulletin, Feb., 1898.

[9] Hinsdale: *Loc. cit.*

[10] E. A. Schäfer and Swale Vincent: Journal of Physiology, May 11, 1899.

[11] In a foot-note the authors state that it cannot be cholin, since its action persists after administration of atropine, whereas they found that the depressant action of cholin is prevented by atropine. It is evident, if the views outlined in this work are correct, that the *dose* of atropine regulates the effect produced, and that physiological tests of this kind are misleading, since all toxic symptoms are due to the functional variations of the single set of organs—the adrenals.

fering from Howell's observation in connection with the rise of pressure. They recall the fact that the infundibular part of the pituitary is mainly made up of gray, nervous matter.

The same authors[12] obtained from decoctions of the infundibular part of the pituitary (thus confirming Howell's observation that this part alone of the gland caused the rise of blood-pressure) "results resembling, in a general way, those of suprarenal extract. They cause quickened respiration, increased heart's action, and ultimately paralysis, commencing in the hind-limbs," facts which they demonstrate by tracings. Yet these experiments were carried on at times with animals under the influence of morphine and curare, both of which drugs may induce, as we have seen, the above symptoms. At other times and besides these two toxics, they injected atropine, an agent which stands among the first of the blood-pressure-raising drugs, through its ability to excite a high degree of suprarenal overactivity. Hence they note that "after the administration of atropine the rise of blood-pressure which is got on intravenous injection of the infundibular extract is enormous and is accompanied by very little slowing of the pulse." As all the experiments include the simultaneous use of two or three of the above agents, the conclusions based on them lose their value for us, except in one connection, which will be referred to later on. In further experiments Osborne and Swale Vincent[13] obtained from a saline decoction of the gland an alcoholic precipitate which produced depressor effects, and with ammonium sulphate, a precipitate which produced pressor effects. The "depressor" effects, which could also be obtained with extractives of any portion of the nervous system and especially of the cerebral gray matter, could not be prevented by section of the vagi.

What can we conclude from this evidence? Gauthier's clinical subdivision of acromegalic symptoms distinctly recalls those produced by any form of active intoxication—provided the suprarenal glands, as herein suggested, are made the active factors of these symptoms. His "erethic" stage is evidently that due to overactivity of the adrenals; the "cachectic" stage,

[12] E. A. Schäfer and Swale Vincent: Journal of Physiology, Sept. 18, 1899.
[13] Osborne and Swale Vincent: British Medical Journal, March 3, 1900.

that of insufficiency. We are brought back to the similarity of these symptoms to some of those observed in exophthalmic goiter, the specific signs of the latter being the missing ones. Why should the latter—the intense tissue-waste, the rapid heart-action of the first stage—be peculiar to Graves's disease? There seems to be good ground for the belief that they represent the highest expressions of suprarenal activity, especially the cramped heart: a fact easily accounted for by the physiological nature of the stimulant, the only truly physiological stimulant so far met with in our inquiry. In thymus we found a product connected with bone- and nerve- nutrition, but capable of incidentally stimulating the adrenals. Have we in the pituitary another physiological stimulant, as in the thyroid, or an indirect stimulant, as in the thymus?

The experiments of Vassale and Sacchi will assist us in clearing this question. Again do we meet with death as the result of removal of the organ; it also followed, we have seen, removal of the thyroid and the thymus. This brings the problem to the common plane of suprarenal insufficiency, if the symptoms are similar to those observed after removal of the other glands. Rigidity of gait, fibrillary contractions, and spasms,—followed by anorexia, depression, and hypothermia,—point to the two familiar stages, however, and suggest that removal of the pituitary is followed by the accumulation of poisons in the organism which it is the organ's function to destroy: a theory which many investigators have advanced. But if they ascribe to the pituitary the rôle of a laboratory for the destruction of toxics, restoration of the laboratory to its normal functions should *alone* insure continuation of the prophylactic process; and the injection of a small quantity of the glandular extractive should not suffice to temporarily eliminate the morbid symptoms unless that extractive stimulate *some other organ* in the body capable of carrying on the prophylactic function. Vassale and Sacchi have not only obtained restoration by this means, but the many experiments just referred to have demonstrated that pituitary extract was essentially a blood-pressure-raising substance which, in the light of our work, means a powerful suprarenal stimulant.

This feature completely transforms the question. Indeed,

we can now see why two stages occur after *removal* of the pituitary. Since we have a stage of suprarenal overactivity, there must have been, as stated, an accumulation of poisons in the organism as a result of the extirpation of the organ. The rigidity of gait, spasms, etc., point to the nature of the poisons: *i.e.*, waste-products of metabolism. The pituitary must, therefore, also be able to stimulate the adrenals, since we now know that the oxidation processes of which they are the underlying factors destroy these toxics. But as there is also a stage of insufficiency in the operated animal, we are normally led to the conclusion that the metabolic products have been more than a match for the adrenals and that the latter have finally succumbed, just as they would have under the effects of any active poison.

Precisely, therefore, as we have in the thyroid and thymus a product capable of stimulating the adrenals, so do we have in the pituitary gland a product capable of stimulating the adrenals. The effects witnessed in the experiments of Oliver and Schäfer, Szymonowicz, Howell, de Cyon, Ott, Hinsdale, Schäfer and Swale Vincent, and Osborne and Swale Vincent, if this be true, are all ascribable to the latter organs. We can readily understand now why Howell had to allow the effects of one dose of extract to pass off before a repetition of these effects could be obtained from a succeeding one. The first dose had brought the adrenals up to a high degree of activity, —perhaps that specific to pituitary extract,—and the next dose could do no better. Such was not the case when the stage of insufficiency was reached, however; here *specificity no longer existed*, and, the larger the dose, the deeper became the lethal tendency: *i.e.*, the suprarenal insufficiency. This is shown by the results of Schäfer and Swale Vincent in this connection.

Again, the experiments of the last-mentioned authors point to the differential effects of various agencies. After the administration of atropine the rise became "enormous": further evidence that they had incited suprarenal overactivity to a degree far exceeding that of which the pituitary extract itself was capable. As to the pressor and depressor effects noted by Osborne and Swale Vincent, it seems probable that they were merely using solutions of different strengths. Yet

their saline decoctions, which produced depressor effects, must have been potent agents. This observation, linked with the fact that cerebral gray matter produced similar effects, is valuable and suggestive, and will serve as the starting-point in our search for the active principle of the organ referred to. For the time being, we can safely, however, formulate the proposition that *the pituitary gland stimulates the secretory functions of the adrenals and thereby enhances the activity of the oxidation processes.*

THE PATHOGENESIS OF ACROMEGALY.

What is the nature of the specific symptoms, independent of those ascribable to the adrenals, to which morbid changes of the pituitary can give rise? We have in exophthalmic goiter the type of a disease brought on indirectly through functional overactivity of the thyroid and adrenals. May we not have in acromegaly a disease also brought on through *excessive* functional activity of the pituitary and the adrenals?

There seems to be good ground for a separation of the morbid phenomena generally ascribed to the pituitary into two distinct, though related, syndromes. Thus, Marinesco,[14] after examining four cases of acromegaly by means of the Röntgen rays, reached the conclusion that, if this disease comes on in adult life, the osseous hypertrophy is of a massive type, while, when it affects adolescents, the bones increase in length as well as in volume. The latter represents the "giant" type of acromegaly. Again, Brissaud and Meige,[15] in a study of the statistics of gigantism, including two personal cases, found that this condition often precedes acromegaly, although both are traceable to the same anatomical process. Gigantism can, however, remain such and not be followed with acromegaly; the latter, on the other hand, can appear alone, since it is by no means always attended with gigantism. The giant type appears during the process of normal growth, while acromegaly can appear subsequent to this process. M. Sternberg[16] goes even so far as to state that gigantism is not a disease

[14] Marinesco: Gazette Hebdomadaire de Médecine, June 18, 1896.
[15] Brissaud and Meige: Nouvelle Iconographie de la Salpêtrière, No. 6, 1897.
[16] M. Sternberg: Zeitschrift für klin. Medicine, vol. xxvii, 1895.

per se, but a condition capable of readily associating itself with other disturbances of nutrition, especially acromegaly. This may be true, since gigantism may not be followed with acromegaly, while the statistics of W. Hutchinson[17] show that 40 to 60 per cent. of these prodigies are also acromegalic. This statistical proportion suggests, therefore, that 40 to 60 per cent. of giants are not cases of acromegaly.

Yet this does not bear very deep examination. Typical giants are really weaklings; while abnormal strength may prevail, this does not last, and they reach an early grave. Indeed, Hutchinson found that the ultimate result was similar in both; the location of the outgrowths and the sexual disturbances are similar, and about the only difference between them that he could detect were the symptoms due to the intracranial pressure of the growth and the more rapid course of true acromegaly as compared to gigantism. The position that seems best to harmonize with the data available is that of Marie,[18] who first described the disease and gave it its name: *acromégalie*. His view has always been that gigantism occurs in the adolescent when the acromegalic tendency is present during the period of growth, whereas if it appears after full development —*i.e.*, in the adult—the hypertrophic process occurs mainly at the extremities of the long bones, due to intense peripheral histogenesis. Further studies have extended these restricted limitations, however, and it is now known that there is not only hypertrophy of the extremities, but also of the bone proper, the voluntary muscles, the cellulo-adipose tissues, the skin, the lymphatics and often of the viscera, the liver, spleen, the kidneys, etc.,—a true histogenesis of practically all tissues.

A logical inference to be drawn from this abnormal development is that the underlying causative factor must be a morbid *overproduction of building elements*. In other words, if the pituitary serves to provide the organism with a building product manufactured by it from elements obtained through food, etc.,—a view in conflict with many prevailing doctrines, even that of Marie, who believes that the pituitary through disease becomes incompetent to neutralize various substances

[17] W. Hutchinson: New York Medical Journal, July 21 and 28, 1900.
[18] Marie: Bulletin de la Société des Hôpitaux de Paris, vol. xii, 1896.

that are capable of causing acromegaly,—it would seem reasonable to suppose that inordinate assimilation of the primary elements and correspondingly excessive production would alone account for the excessive growth witnessed. But this apparently involves another conflicting feature, as against the many theories in which disease of the pituitary is rendered responsible for loss of function and resulting neuroses, auto-intoxications, vasomotor disturbances, asphyxia of extremities, etc.: *i.e.*, the need of *overactivity* of the pituitary and simultaneously of the adrenals to satisfactorily account for the increased production of cellular elements witnessed.

Tamburini,[19] after an analysis of twenty-four cases in which post-mortem examination had been made, concluded not only that "in all *typical*[20] cases of acromegaly a growth of the pituitary prevailed, but that there was at first hypertrophy of the gland, *with exaggeration of its functions* and, later on, abolition of these functions."

Harlow Brooks,[21] after a careful study of the entire subject, refers to the feature in point in the following words: "It is manifest that the only reliable key to the unraveling of this rather chaotic mass of morphological alterations in the hypophysis obscuring the pathogenesis of acromegalia is on the *basis of function.*" He then shows the solidity of this view in the following lines: "By the process of elimination, in the last chapter, the field of pituitary lesions was virtually narrowed down to the second or hyperplastic class of changes, and these are the true and essential lesions in acromegalia. Besides the reasoning from the method of exclusion, there are also positive data supporting this theory, for, in several cases, observers have interpreted the results of their examination of the pituitary changes as hyperplasia or adenoma. These data furnish the key to disentangle the discordant observations, and if we adhere to these results the subject seems clear.

"Against the view of the increased function and hyperplasia theory, however, stand the observations of the cases of

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[19] Tamburini: Rivista Sperimentale de Freniatria, p. 559, 1894, and p. 414, 1895.

[20] All italics are our own.

[21] Harlow Brooks: Archives of Neurology and Psychopathology, vol. i, No. 4, 1898.

sarcoma and morphologically similar neoplasms of the hypophysis in acromegalia. These observations greatly outweigh in number the instances recorded as hyperplasia and adenoma, and, in fact, constitute the great bulk of evidence in cases examined microscopically.

"If we can show, however, that there are good reasons for believing that these instances of sarcoma have been wrongly interpreted and are really examples of hyperplasia, the pathogenesis of acromegalia stands out clearly on a basis of harmonious data. This is not difficult. The mistake of confounding hyperplasia and even adenoma of the gland for sarcoma might be very easily committed, indeed. The glandular structure of the hypophysis is rather atypical, its cells are small and rather densely huddled together, and the connective tissue is very scanty. Consequently in an hyperplastic overgrowth the appearance resembles, very closely, indeed, a sarcoma of the small round-celled or lymphosarcomatous type." The author then refers to several cases in which he had at first considered the enlargement of the pituitary as due to small, round-celled sarcoma, and which, under the guidance of the idea of hypersecretion, gave every evidence of hyperplasia. He furthermore noted that "these so-called sarcomata of the hypophysis in acromegalia are lacking in two rather predominant traits of sarcoma," and remarks: "We should expect evidences of metastasis and comparatively rapid growth, yet both of these characteristics are absent. With the exception of a few cases, the course of acromegalia is notoriously slow, gradual, and chronic, and extends over a number of years. Such a course in the growth of a sarcoma would be a rather striking exception to the rule.

"The hypersecretion theory, as far as I am able to learn, was first brought forward by Tamburini, but I feel like stating it much more positively." Indeed, Tamburini had also affirmed that, while one is justified in concluding that the lesion that is constantly met with in autopsies upon typical cases is tumor of the pituitary body, this usually assumes the form of adenoma, the next of kin to hyperplasia of the glandular tissues.

Whether, as Marie says: "acromegaly is gigantism in the adult," or "gigantism is acromegaly in the adolescent," we are

always dealing with acromegaly, and this fact, coupled with the probability emphasized by the above data that there is always overactivity of the pituitary when either of these two conditions is present, may help us to ascertain the nature of the symptoms of pituitary origin.

Whether they appear in the adolescent or in the adult, the earlier symptoms of acromegaly are always insidious. Enlargement of hands, feet, or head may constitute the first indications of disease and be perceived only through the unmistakable tightness which the shoes, gloves, or headgear may assume. There may be some headache, rheumatic pains, or impairment of vision, and the disease may be considerably advanced before it is recognized as such. In a case reported by Leszynsky,[22] for example, the patient had frequently been the object of jocular remarks concerning the size of his feet and hands before he suspected disease, and visited the hospital because of his vision, which had become "blurred" a year before. In another case reported by Johnston and Monro[23] acromegaly followed parturition. A swelling around the eyes was the first sign, and never disappeared. Shortly afterward enlargement of the face, hands, and feet became apparent. About two and one-half years later her vision began to fail, and it was about this time that she first complained of headache, which, from being paroxysmal, soon became constant. We have in these two instances, among the many that have been reported, clearly defined symptoms of hyperplasia of the pituitary. If now excessive activity of the latter enhances suprarenal activity and correspondingly increases oxidation, we should, even among these earlier manifestations, find evidence of this excessive oxidation.

While the suprarenal phenomena of the earlier stage are not always referred to in all accounts of cases, they are given in many, and their enumeration will suffice to at once recall their relative frequency: *i.e., excessive* and *sometimes ravenous appetite, thirst, polyuria, a full and hard pulse*, and, often, *cutaneous hyperæsthesia, a sensation of abnormal superficial heat*, and, after the case has progressed some time, *muscular hypernutri-*

[22] Leszynsky: Medical Record, March 4, 1899.
[23] Johnston and Monro: Glasgow Medical Journal, August, 1898.

tion. All these symptoms except the latter are witnessed in exophthalmic goiter, though muscles do not show, at first, the general emaciation which is observed in this disease. Yet there is every reason to believe that the activity imparted to the adrenals by the secretion of the pituitary is less marked than that caused by the thyroid secretion. Hinsdale, in his essay, based on a study of one hundred and thirty cases of acromegaly reported in literature, refers to the muscular symptoms as follows: "The muscular system varies in development with the type and stage of the disease. Naturally, the strength is great in the early period and particularly in the giant form. . . . The facts that the disease has existed for a considerable time when the cases are reported and that they apply to physicians for relief of symptoms explain why muscular power is commonly noted as weak, as a rule. . . . As the period of decadence sets in, muscular atrophy renders the patient quite powerless, and cardiac dilation adds to the weakness of the circulation. *Tremor*[24] is not unusual in acromegaly."

The cachectic stage as typically indicates the part played by the adrenals in the morbid process. Besides the *muscular weakness* just referred to, there is often marked *sensitiveness to cold.* The reduced vascular pressure is shown by *increased rapidity and weakness of the pulse;* and examination reveals a dilated heart. Brooks, referring to the lesions of the vascular system, says: "In short, the vascular lesions are found in their most exquisite type in those portions of the body where the circulation is slowest and where *capillaries* are most numerous." *Exophthalmos* is also witnessed in many cases, including the slow lid-motions, all probably due to the muscular debility; *sweating* in common, and is doubtless ascribable to the weakness of the muscular elements of the sweat-glands. *Glycosuria* is commonly observed. Referring to the lesions of the skin, Brooks also states: "Macroscopically, the skin in these areas is considerably thickened; the surface is *rough* and often fissured. A general *brownish pigmentation* is present in the average case, which, at times, strongly resembles that found in Addison's disease."

[24] The italics are our own.

That the suprarenal glands should be credited with the great majority of the symptoms now ascribed to the pituitary alone is evident. Indeed, the remaining signs that might be attributed to the latter may be still further limited in number. Among those to be excluded are the various phenomena due to pressure of the enlarged pituitary. The headache is one of these, although its severity is probably increased during the first stage by the cerebral hyperæmia caused by overactivity of the adrenals. The many symptoms of which the visual apparatus is the source, excepting those due to the loss of local muscular power already referred to, are also ascribable to pressure of the hypertrophied pituitary. The senses of smell, taste, and hearing are occasionally involved.

Mental phenomena are frequently observed, but, as a rule, they are credited to the mortification suffered by the patient because of the deformities of features and form which the disease brings on. They appear to us to merit a far more conspicuous position in the pathology of acromegaly than they are given, owing mainly to the light their close connection with so manifestly a trophic disorder may shed upon the mental diseases in general. Do they belong to the domain of the pituitary or to that of the adrenals? We have seen that mania is associated with suprarenal overactivity while melancholia is observed during the stage of insufficiency.

In referring to Blair's case of persecutory mania associated with acromegaly,[25] and to his remark that but three cases had come to his knowledge, one in England and two on the Continent, R. H. Hutchings[26] likewise emphasizes the fact that sufficient attention has not been given the mental symptoms of the latter disease. He also reports two instances, one of which, a typical case, is particularly interesting to us, since death occurred before the second—or cachectic—stage had been reached. Unfortunately the pathological histology of the brain is not given, but the statement that it "was compact, of good weight and firm," while no reference is made to peripheral pressure lesions in the neighborhood of the enlarged

[25] Blair: Journal of Mental Science, April, 1899.

[26] R. H. Hutchings: Archives of Neurology and Psychopathology, vol. i, No. 4, 1898.

pituitary, suggests that the mental disease could not be attributed with justice to pressure of the growth. This is further sustained by the fact that visual disturbances, so frequently noted, are not referred to, the eyes being "deeply set and small." The case was, mentally, one of "mild, gradually-increasing dementia." The second case is an instance of feeble-mindedness with marked amnesia, with no tendency to irritability, as in the former. With this feeble-mindedness, however, is associated another disorder (one probably due, as we have seen, to the sudden production and accumulation of waste-products, and referable, therefore, to the adrenals, or, rather, to exacerbative suprarenal overactivity): *i.e.*, epilepsy. That mental shocks of various kinds often initiate exophthalmic goiter is well known. The patient had never been very bright. At the age of *seventeen* he had been frightened, and this marked the first of his fits, which have continued ever since: *i.e.*, twenty-seven years. As the acromegaly began about seventeen years after the onset of the epileptic seizures, it appears possible that this long-continued overnutrition of the pituitary may have been the cause of his acromegaly—typical not only in respect to its specific symptoms, but also to those distinctly traceable to the adrenals. Three years before the report the more acute symptoms began to appear, and when Dr. Hutchings's paper was published he had had fewer epileptic seizures than formerly, but amnesia was more marked: both signs that the cachectic stage—*i.e.*, that of suprarenal insufficiency—was approaching. In a very similar case, in which weak-mindedness also prevailed, though no epilepsy is referred to, Roxburgh and Collis[27] found at the necropsy *softening* of an enlarged pituitary gland.

Valuable in this connection is one of two cases of acromegaly with imbecility in adolescents reported by W. G. Shallcross[28] after a daily observation during a period of nearly six years. In this case, now aged 18 years, rated as a "high-grade imbecile" when admitted into the Pennsylvania Training-school, a marked change, both mental and physical, appeared at the age of fourteen years, and a year later the signs

[27] Roxburgh and Collis: British Medical Journal, July 11, 1896.
[28] W. G. Shallcross: Philadelphia Medical Journal, April 20, 1901.

of acromegaly appeared. He then began to grow rapidly, and *in one year* had nearly reached his present size, 6 feet, 3 inches. At sixteen years and ten months he weighed 210 pounds. Yet a Röntgen-ray examination showed "a uniform hypertrophy, merely an exaggeration of the normal state." Here, again, we find evidence of suprarenal overactivity, though none of the pressure symptoms—headache, etc.—are as yet present. The arterial tension is increased, the hyperidrosis of peripheral vascular pressure is present, the apex-beat is forcible, and there is increasing polyuria—March 10th, for instance, 2400 cubic centimeters daily, and October 15th, 6810 cubic centimeters daily. That the vision is becoming impaired is also suggested by an examination of the eyes by Dr. Thorington, who found double optic atrophy and other signs pointing unmistakably, with the general symptoms, to a growth of the pituitary. The predominating sign in this case, however, is *marked dullness over the upper portion of the sternum*, indicative, as shown by Erb, of an enlarged thymus.

These few illustrations will suffice to emphasize two ruling factors in the study of this question: (1) that the adrenals and the pituitary are interdependent, and (2) that acromegaly may be the result of more than one pathogenic factor. In Hutchings's second case, for instance, there is every reason to believe that an already inadequate, and therefore vulnerable, pituitary, as shown by the patient's mental torpor, traced back to his childhood, underwent morbid development under the influence of the adrenal overactivity to which the accesses of epilepsy point. The normal dense vascular supply of the pituitary readily shows that such a process is possible if its physiological resistance is below the normal standard. Unduly stimulated itself by overoxidized blood, it may thus have been able to overnourish the various structures under its functional influence. The various tissues—bone, muscles, etc.—involved in such cases are developed to an abnormal degree, the whole process being further sustained indirectly by the suprarenal overactivity, which affords a corresponding and necessary increase of oxygen to insure nutritional metabolism. We thus have a form of acromegaly directly due to suprarenal overstimulation of the pituitary, in which, as in Hutchings's case, a structurally

weak organ first undergoes the causative hypertrophy, then finally yields by retrograde metamorphosis to the undue and continuous labor imposed upon it. But during all its period of overgrowth and overactivity the pituitary had in turn stimulated the adrenals, thus establishing a vicious circle, with overwork of both organs as result.

That this conception of the pathogenesis of the disease is based on solid foundation is shown by the experimental use of pituitary extract by Mairet and Bosc[29] in twenty-one epileptics, administered by the mouth or by subcutaneous injection. The number of seizures was not only increased, but a state of mental exaltation appeared which, in some of the cases, was totally different from any mental aberration that they had previously shown.

As to the second stage, here, as elsewhere, the pituitary merely yields to the overwork imposed upon it, undergoes deterioration,—not a mere return to normal conditions, but either softens, as in the case recorded by Roxburgh and Collis, or undergoes the far more common process of fibrous induration. The suprarenal glands then not only fail to receive the additional stimulation resulting from the overactivity of the pituitary, but they lose the normal support which the latter had afforded them. Thus seems to be inaugurated not only the stage of suprarenal insufficiency, but also the cachectic stage of the acromegalic syndrome itself.

If all this is true, we should have evidence of suprarenal insufficiency, as manifested through its cardinal expression,—myxœdema,—along with those of insufficiency of the pituitary, since reduced functional activity of the adrenals should correspondingly impair the nutrition of both the other organs. That simultaneous and sufficiently advanced inadequacy of all three sets of organs gives rise to but one result—*i.e.*, myxœdema—is well shown by two cases in which necropsies were performed by Ponfick[30] and quoted here purposely from an abstract to show the solidity of the position taken: "One patient died early in the course of the disease from inter-

[29] Mairet and Bosc: Archives de Physiologie norm. et path., July, 1896.

[30] Ponfick: British Medical Journal, June 16, 1900, from Zeitschrift für klin. Medicin, Bd. xxxviii, H. 1.

current pneumonia, the myxœdema itself being in a mild and *early stage.*[31] The changes found in the thyroid gland were of two kinds, namely: interstitial inflammation[32] and *pure atrophy.* In the above case there were found an atrophy of the pituitary (its size being three-fourths that of the normal) and a marked involvement of its blood-vessels. Some parts of the thyroid gland showed a marked colloid change. On examination of the pituitary body an *almost complete loss of the glandular substance* was found, together with marked induration of the fibrous stroma, and the *resemblance between the pathological changes in the two glands* was striking. The *post-mortem* examination in the second case also showed destruction of the glandular elements of the pituitary and a growth, in its stead, of fibrous tissue. Ponfick observed that these and other recorded cases go far to show that in a good many cases of myxœdema where a considerable portion of the thyroid may be found intact the hypophysis is so changed and its glandular substance so much destroyed that it seems probable that *the morbid changes had begun in the hypophysis before there were any alterations in the thyroid body.*"

The sequence of events is clearly indicated in these cases. But why did they not give an early history of acromegaly? For the same reason that some cases of exophthalmic goiter lapse into the second, or cachectic, stage soon after the onset of the first: *i.e.,* because their suprarenal glands were morbidly inadequate, rapidly yielded, and became insufficient through the combined effects of the thyroid and pituitary secretions which their own overactivity had brought on. Once overnourished for any length of time, the tendency of tissue is not to resume its normal histological organization, but to degenerate, as is well shown in the case of the heart-muscle. All three organs, therefore, underwent retrograde metamorphosis. This is proven by the fact that the progress of either disease is not impeded when the three organs involved in such cases are adequate and able to withstand for a sufficiently long period, and simultaneously, a high grade of overstimulation. The typical syndrome of thyro-suprarenal overactivity, exoph-

[31] All italics are our own.

[32] Doubtless due to the toxic process.—S.

thalmic goiter, then appears along with the pituitero-suprarenal symptom-complex, acromegaly, in the same case. Witness the case reported by G. R. Murray.[33] The patient presented the characteristic signs of acromegaly,—enlargement of the bones and tissues,—and those of exophthalmic goiter,—the enlarged thyroid, early exophthalmos, rapid heart-action, etc. Hinsdale[34] refers to five such cases found in literature.

Again, the influence of overactivity of the three sets of organs in bringing on the first stage of acromegaly is well illustrated in a case described by Pearce Bailey.[35] Though the patient was a woman 65 years old, the first signs of acromegaly had only occurred five years before her death (due to an intercurrent pulmonary disorder) and were still plainly those of the first stage. At the autopsy the thyroid was found to be nearly three times its normal size; and "microscopical examination showed that the gland-substance was generally normal, although in places the acini were much dilated and filled with colloid material." The pituitary was more than eight times its normal weight. The posterior, or neural, lobe presented no structural alteration; while the anterior, or glandular, lobe was very vascular, the *capillaries being dilated and filled with blood.* The history of the case, only obtained after death, is very brief, and signs of suprarenal overactivity suggesting exophthalmic goiter are not mentioned. But the causes of death, "uræmia and pulmonary congestion," are, as we will see, direct expressions of the capillary *centrifugal pressure* that intense activity of the adrenals can produce, the existence of which is shown in the pituitary itself by *dilation* of its vascular net-work. Bailey also refers to a case of Van Horne Norrie's, in which phenomena recalling the earlier symptoms of acromegaly were found after death, associated with a pituitary "enlarged to three or four times its natural size, in which *an extensive hæmorrhage* had recently taken place." During life another sign of peripheral capillary engorgement, wide-spread paræsthesia, had been present, evidence

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[33] G. R. Murray: Edinburgh Medical Journal, Feb., 1897.
[34] Hinsdale: *Loc. cit.*
[35] Pearce Bailey: Philadelphia Medical Journal, April 30, 1898.

of another vicious circle in which the organs enhanced each other's activities.

Resuming the consideration of the mental phenomena observed in practically all cases of acromegaly—hardly perceptible in some and very marked in others—to the query as to whether they can be ascribed to the adrenals or the pituitary, the only answer possible so far is the following: The above evidence tends to show that intense suprarenal overactivity can so engorge the cerebral capillaries as to cause a disruptive hæmorrhage in an enlarged pituitary body. Whether the mental symptoms are ascribable to the cerebral hyperæmia or to the impairment of certain functions *of the pituitary itself* or to both it is as yet impossible to say. We can only recognize, for the time being, that, with the stage of acromegaly in which the adrenals are overactive, the mental aberration is of a kind usually associated with cerebral hyperæmia and which may in some cases of acromegaly assume considerable violence. Thus, in Tamburini's case[36] some years after the onset of the acromegalic symptoms the patient, a young woman, manifested delusions of persecution with violent excitement, terminating in dementia. In another instance, reported by H. W. Coe,[37] the patient, a woman aged 50 years, finally assumed such homicidal proclivities that she was committed to an asylum. In Tamburini's case a very large pituitary was found, an adenoma; Coe's case was still living and in the asylum at the time of the report. We may perhaps acquire more light in this connection through the next feature to be analyzed: *i.e.*, the relationship between the thymus and acromegaly.

We have seen that in Shallcross's case of acromegaly in an adolescent imbecile there was marked dullness over the upper portion of the sternum. Klebs[38] and Erb[39] have emphasized the importance of the persistence of the thymus in acromegalic subjects, and "Erb's sign," dullness on percussion over the upper third of the sternum, was once deemed an important diagnostic feature of the disease. It gradually lost

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[36] Tamburini: *Loc. cit.*
[37] H. W. Coe: Journal of the American Medical Association, Dec. 3, 1898.
[38] Klebs: Allgem. Pathol., vol. ii, 1889.
[39] Erb: Münchener med. Wochenschrift, No. 24, 1894.

its weight, however, as many other valuable hints have in medicine, simply because it did not happen to fit every case, and notwithstanding the fact that the organ had been found persistent at autopsies and in some cases enlarged, by a number of pathologists. The form of acromegaly due to suprarenal overactivity just discussed seems totally disconnected from the thymus; but this does not mean that a persistent thymus should not play the main rôle in the causation of a second form: *i.e., one prevailing in adolescents or young adults.*

Percy Furnivall,[40] in an analysis of 17 cases of acromegaly, found that the thymus was absent in 7, but *hypertrophied* in 3, and *persistent* in 7: *i.e.,* nearly 60 per cent. of the cases. The only constant associated changes appeared to be in the pituitary body. At the same meeting of the Pathological Society, Rolleston[41] referred to the case of a woman, aged 35 years, who had shown symptoms of acromegaly for three years. "She suffered from optic atrophy due to the pressure of the tumor; headache, which was intense at times; and transient glycosuria. The skeletal changes were quite characteristic." The patient died "after an epileptiform fit." . . . "The pituitary tumor was a round-celled sarcoma the size of a walnut." . . . While the thyroid gland appeared normal, "the thymus gland was persistent, and was much in the condition of that *of a child before the changes of involution had set in.*" We have here not one phenomenon, but two distinct manifestations of as many individual functions: Suprarenal overactivity, as represented by the epileptiform fit; excessive activity of the pituitary, as represented by the acromegalic symptoms.

Why do we not have in the above case a third manifestation traceable to the—presumably active—thymus? We have seen, when considering the physiological action of the thymus, that this organ and the adrenals are interdependent as long as the activity of the thymus lasts: *i.e., until puberty.* But *after* puberty, and when the thymus becomes normally atrophied, are the adrenals deprived of this stimulus? To answer this question negatively would be to concede that after puberty the bodies that furnish phosphorus in organic combination, and

[40] Percy Furnivall: Lancet, Nov. 6, 1897.
[41] Rolleston: Lancet, Nov. 6, 1897.

which we have traced to the thymus, are no longer produced in the organism. Such an assertion is contradicted by considerable clinical evidence and by the pathological phenomena of the cases of acromegaly in which the thymus is not persistent. There must be, therefore, a successor to the thymus capable of continuing actively or passively its physiological functions. Especially must this be the case since, as we have seen, impairment of the functions of the thymus and of the adrenals underlies the disorders of nutrition which inhibit the development of the cerebro-spinal, nervous, and osseous systems—all structures involved in acromegaly. It would appear, therefore, that, if overactivity of the pituitary gland is the source of acromegaly, this organ should assume at least some of the functions of the thymus at puberty.

That this conclusion is justified seems sustained by considerable testimony; it would remove the obstacles that are themselves as strongly supported by existing data. Gigantism, for instance, can thus assume the apparent autonomy observed in some cases. A persistent thymus overlapping an efficient pituitary, *plus* adrenals that are necessarily overactive through the extra stimulus which the additional organ procures, make up a physiological trio fully capable of causing the additional formation of cellular elements which excessive growth involves. We know that when overgrowth is a feature of acromegaly it mainly appears in adolescent subjects or young adults, while it is the exception when the disease appears in middle-aged subjects or later. Indeed, the stature of some of the latter is sometimes shortened by scoliosis. Again, there is a marked distinction between the forms of acromegaly observed during youth or adolescence and that occurring after maturity: a feature emphasized by Woods Hutchinson.[42] The overdevelopment of the former is comparatively symmetrical; the overgrowth in the latter mainly shows itself at the points of least resistance: *i.e.*, the extremities, hands, feet, nose, lower jaw, etc.

It seems probable, however, that, while Maximilian Sternberg's view that there are two forms of gigantism, the first

[42] Woods Hutchinson: *Loc. cit.*

normal, mere overgrowth; the second pathological, the former predisposing to the latter, prevails, true gigantism (not the mere overgrowth of very tall subjects) is probably rare without acromegaly. Marie's view that "gigantism is acromegaly of the adolescent," while "acromegaly is gigantism of the adult" probably comes nearer the actual condition present in both forms. This is suggested by the fact that, if the pituitary does succeed to some of the functions of the thymus and the latter persists sufficiently long to add materially to the stimulating effects of the former upon the adrenals, a vicious circle of overnutrition is formed through which the longevity of the thymus is prolonged and sustained until softening, fatty degeneration, or fibrosis—*i.e.*, insufficiency of either of the three sets of organs—initiates the cachectic stage. This is clearly indicated by the terminal symptoms that attend cases of true gigantism. "Myth and popular impression to the contrary," says Woods Hutchinson,[43] "giants are a short-lived, feeble-minded, weak-bodied race." This nevertheless leaves us free to distinguish at least three main forms of acromegaly from the standpoint of pathogenesis:—

1. A form due to overnutrition of predisposed pituitary through continuous overactivity of the adrenals, maintained, in turn, by a chronic toxæmia.

2. A form due to persistence of the thymus and brought on by overstimulation of the adrenals by the phosphorus-containing thymic secretion, resulting in overnutrition and hypertrophy of the pituitary.

3. A form due to morbid processes—tumors, etc.—in the pituitary itself.

THE FUNCTIONAL RELATIONS BETWEEN THE ANTERIOR AND POSTERIOR PITUITARY BODIES.

We have seen the remarkable observations of Bourneville and Katz in respect to the absence of the thymus in idiots. If we couple this feature with the clinical evidence attesting that the pituitary gland is the growth-center of the organism, we can analyze and perhaps find the connection between these organs and between the two pituitary lobes.

[43] Woods Hutchinson: Quoted by Hinsdale, *loc. cit.*

E. de Cyon,[44] after an exhaustive experimental study of the pituitary gland, reached the conclusion that this organ, like the thyroid, possessed two functions: the one mechanical and the other chemical. Unaware, of course, of the rôle played by the suprarenal gland as given in the present work, he carefully recorded the effects of mechanical pressure upon or electrical stimulation of the pituitary. He found that either of these sources of irritation immediately gave rise to variations of blood-pressure and to a notable *increase of power and slowing of cardiac action*, and ascribed these phenomena to excitation of the vagus, which nerve was supposed by him to cause vasodilation of the thyroid, followed, in turn, by depletion of the cerebral circulation.

From our standpoint it seems more probable, as we have seen, that an entirely different process occurs: *i.e.*, that the pituitary directly stimulates the suprarenal glands. Even in this connection, however, de Cyon's experiment is a valuable one, especially when connected with one performed by Howell with pituitary extract and which showed that extract obtained from the posterior lobe *alone* contained the blood-pressure-raising substance. While de Cyon's observation enables us to distinctly prove a direct connection between the pituitary body and the adrenals, Howell's suggests that the posterior lobe must be the one functionally connected with the latter organs. Indeed, so marked was the suprarenal stimulation thus produced that, although unaware that he was witnessing effects of suprarenal origin, the resemblance suggested itself to him. Thus, he says: "These extracts injected into the normal animal with its vagi intact cause a very pronounced slowing of the heart-beat, similar to that caused by suprarenal extracts, but lasting a much longer time. The heart-beat is not only slowed, but is considerably augmented in force, as is shown by tracings taken with a Hürthle manometer."

If the anterior lobe does not contain a substance capable of producing similar effects, what can its functions be? It seems disconnected from the posterior in this particular, though related with the infundibular walls by connective tissue and

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[44] E. de Cyon: Archives de Physiologie, July, 1898.

many vessels, arterial and venous. This lobe—unlike its mate, in which are found neuroglia, nerve-cells and epithelial-cell tubules that contain a colloidal material—is subdivided into numerous cavities, or vesicles, that vary in size and the walls of which are lined with acini, made up of epithelial cells. Some of these acini, especially those near the posterior lobe, also contain a colloidal substance. The glandular elements are surrounded by a close net-work of lymphatics and capillaries, which, as we have seen, may become the seat, not only of intense engorgement, but also of hæmorrhage. The anterior lobe, on the whole, recalls the thyroid in histological structure, and several investigators—Rogowitsch, Gley, Stieda, and others—have observed hypertrophy of its elements when the thyroid was removed. In a large proportion of the cases of acromegaly it is also this lobe that exhibits the morbid changes: an analogy which suggests that its secretion might also be similar to that of the thyroid. Is this the case?

If the secretion of the anterior lobe were similar to that of the thyroid, there should also be considerable analogy between the products of these organs and the secretion of the thymus, since, as we have suggested, the pituitary appears to be, in this particular at least, one of the successors of the latter. This involves the presence, in all three of the organs, of the chemical bodies upon which the hardness of the osseous frame-work depends, since the preponderating phenomenon of disease of the anterior lobe of the pituitary is bony overgrowth, while removal of the thymus, as shown experimentally, is followed by softness and bending of the bones. The administration of thyroid extract in cretinism, on the other hand, is followed by overgrowth, but with coincident softness of the bones: a feature which in itself seems to negate the presence of phosphorus in the thyroid secretion.

R. Hutchinson's[45] analyses of the thyroidal colloid have shown that the proportion of phosphorus was 0.4 per cent., all contained in a non-proteid part separated from the colloidal substance by the action of boiling acids or the gastric juice. Baumann's iodothyrin owes its activity to this non-proteid con-

[45] R. Hutchinson: Journal of Physiology, Dec. 3, 1896.

stituent, according to him; but he also states that iodothyrin contains practically all the iodine found in thyreoglobulin,—a proteid of which he had just said[46]: "It contains the whole of the iodine in the gland and is the seat of the active constituent." Hence iodothyrin not only contains all the iodine of the colloid material, but also its phosphorus. In the paper last mentioned, however,—written over four years after that in which he refers to phosphorus,—the various bodies found in small amounts in the thyroid—xanthin, hypoxanthin, inosite, creatin, sarcolactic acid, etc.—are mentioned, but phosphorus is not referred to. He further states that, "with the exception of iodothyrin, no substance has yet been isolated from it to which therapeutic properties can certainly be ascribed." This in no way invalidates the evidence adduced as to the presence of arsenic, discovered by Armand Gautier, since Hutchinson evidently did not look for it, but it coincides with the clinical observation that, while thyroid extract increases the growth of young cretins, it fails to supply them with phosphorus. The small amount of phosphorus obtained is doubtless that concerned with the metabolism of the glandular tissues themselves; and it may be concluded that the thyroid secretion does not supply this metal to the tissues with which it is concerned, and that the rôle of phosphorus in the thyroid itself is limited to its use in the intrinsic cellular metabolism of this organ. Of course, the output of phosphoric acid is greatly increased after the ingestion of thyroid extract, but we have in this fact only further testimony as to its ability to enhance the activity of the pituitary, this organ, in turn, stimulating the adrenals, thereby increasing oxidation. Evidently iodine remains the predominating thyroidal product.

That the thyroid and the pituitary differ in this particular is clear. The connection between the pituitary and the various pathological processes reviewed, and especially the influence of this organ on bone overgrowth obviously points to the presence of phosphorus in its secretion. This is verified by de Cyon, who isolated a phosphorus-containing substance from the pituitary which he termed "hypophysin." He obtained *from*

[46] Baumann: Practitioner, April, 1901.

this substance, when injected into the veins of animals, effects identical to those previously referred to when the organ was electrically stimulated or touched: *i.e.*, it caused *slowing of the heart's action* and *increased vascular pressure*. He furthermore obtained clinical results with it which led him to conclude that "mental disorders, cephalic pains, and irregularities of the heart-functions are the irrefutable results of impaired function of the hypophysis," so active did his phosphorohypophysin prove in the particular symptoms mentioned. The effects might be ascribed to the property common to all toxics, —of stimulating the adrenals; but this could not hold in the presence of the results of pressure on the gland and the collateral testimony previously adduced herein.

Notwithstanding the fact that their organic active constituents are totally different, we have ascertained that there is a functional relationship between the pituitary and the thyroid. The former organ may become enlarged after removal of the latter (Rogowitsch, Stieda, Gley), or during myxœdema (Boyce and Beadles, Comte, Grón), or in cretinism (Bourneville and Bricon, Dolega, Niépec, Osler), after thyroidectomy (Kocher), or in goiter (Comte, Mitchell and le Count),[47] while de Coulon,[48] in a careful study of the thyroids and the pituitaries of five cretins, found a similar atrophy of both organs in each instance. As both lobes contain acini in which colloidal substance is to be found, and as the anterior lobe is the more glandular of the two, while also that most frequently involved vicariously when the thyroid becomes incompetent, it stands prominently as the one upon which the compensatory function should devolve.

When this question of compensation is at all searchingly scrutinized, however, it is soon found wanting. In the first place, its claims are based only upon more or less marked fluctuations in the dimensions of the pituitary as compared to those of the thyroid. While there is considerable parallelism between these organs, both in hypertrophic and atrophic processes, owing to hypernutrition and hyponutrition of both through general disease, such parallel variations cannot be con-

[47] Mitchell and le Count: New York Medical Journal, April 29, 1899.
[48] De Coulon: Virchow's Archiv, vol. cxlvii, p. 53, 1898.

sidered as compensative. Nor can enlargement found *post-mortem* in cases of goiter, exophthalmic goiter, etc., be regarded as the result of *ante-mortem* vicarious excessive work, since the hypertrophic process may have occurred during a primary stage of overactivity and the pituitary have remained in its enlarged condition, though perhaps histologically modified. Thus, in his analysis of 36 cases of acromegaly in which the relative conditions of thyroid and pituitary were noted, Hinsdale found that, while the pituitary was diseased in all, 13 thyroids were hypertrophied, 11 were atrophied, and 12 were normal. Even cases of myxœdema in which an enlarged pituitary is found prove nothing, since the enlargement may have occurred before the myxœdematous process, along, perhaps, with unnoticed symptoms, the adrenals having soon lapsed into insufficiency and reduced nutrition of the thyroid tissues: the starting-point of the myxœdema.

Of great value in this connection are the results observed after experimental extirpation of the thyroid gland in animals, especially if analyzed through embryological data. Thus, Rogowitsch, among other investigators, noted enlargement of the anterior lobe after extirpation of the thyroid in animals. If the fact, pointed out by Andriezen, that both the thyroid and the pituitary originate from a common region, the ectoderm of the primary oral cavity, is coupled with the view herein advanced, that the thyroid supplies a substance which directly stimulates the adrenals, these experimental results may easily be accounted for. Indeed, to stimulate is to energize,—*i.e.*, to enhance the tone of organic structures; to remove the thyroid, therefore, is to eliminate the tone-giving function of the adrenals; the pituitary, especially the anterior lobe, being an exceedingly vascular organ, relaxation of its vessels means passive engorgement, followed by the enlargement observed by Rogowitsch and others. Under these conditions it becomes apparent that *a morbid change in the thyroid may implicate the pituitary without bringing compensation into the process.*

Indeed, a similarity between the secretions of these two organs is negated by the strongest kind of evidence besides that already adduced. Iodine, for instance, being undoubtedly the main constituent of the thyroid secretion, and phosphorus

that of hypophysin, the teachings of chemistry are peremptory, since iodine and phosphorus, when combined, either form a di-iodide (P_2I_4) or a tri-iodide (PI_3), *both solid bodies.* This clearly shows that these elements cannot be considered as the basis of physiological reactions in which any considerable quantity of both would be actively engaged. Again, Andriezen, as the result of his exhaustive investigation, says: "It must be remembered that the pituitary belongs both anatomically and physiologically to the *central nervous system,*[49] while the thyroid belongs to the *respiratory* function of the *blood-vascular system, and thereby to the tissues generally.*"

We could easily, with all these data, arrive at a final conclusion by contenting ourselves with the mere statement that Andriezen's researches indirectly sustain the view that, while the pituitary supplies the nervous system with phosphorus in organic combination, the thyroid, by its iodine constituent, stimulates the adrenals and thus insures an adequate supply of oxygen. And this would plausibly account for the various phenomena witnessed in connection with the morbid process of either of the organs involved. Still, the pituitary is not composed of one lobe, but of two, and such a conclusion would involve the acceptance of both lobes as chemically and physiologically similar, or of one of them as alone active, the other being classed as vestigial. Ample clinical evidence shows that the anterior lobe is physiologically active in some way,—notwithstanding the inertness of its extractives,—while the posterior lobe has been shown by Howell, Schäfer and Vincent and others, to contain very active constituents. The only course to pursue, in view of these facts, is to consider that both lobes are active, either jointly, in carrying out a single function, or singly, each having a separate rôle in the organism.

The final conclusions to which Andriezen arrives, read in the light of the functions which, to us, seem to be those of the adrenals, strikingly confirm the existence of a physiological relationship between the pituitary and the latter. To give the author's remarks their full value, they are quoted in full: "The main conclusions from the above lines of investigation all point

[49] All italics are our own.

to the important trophic influence of the pituitary gland on the central nervous system of vertebrates," . . . which, "in more definite terms, means *(a)* enabling them to take up and assimilate oxygen from the blood-stream and *(b)* to destroy and render innocuous the waste-products of metabolism, and that at root these two functions are intimately related and are really at root part of one process (vital, or biochemical), an adequate assimilation of oxygen by the nerve-tissues securing an adequate destruction (by oxidation) of the waste-products." Of course, Andriezen here does not distinguish between the two lobes: *i.e.*, he refers to both jointly.

"The predicable results of the ablation or destruction of the gland would, therefore," continues this investigator, "be those due to *(a)* a malassimilation of oxygen by the nerve-tissues, and simultaneously *(b)* an insufficient destruction, and, therefore, accumulation of waste-products, thus bringing about a rapid nutritional failure and death of the central nervous system. In general terms, we would, therefore, expect in the animal:—

"1. Depression and apathy (the commencing failure of activity of the nerve-centers), and

"2. Muscular weakness (the first peripheral effect).

"3. Loss of fine co-ordination and equilibration (correlated to Nos. 1 and 2), and

"4. The development of twitchings and irregular contractions (spasms) of the muscles (in relation to the further progress of nutritive failure of the nerve-centers).

"5. A want of sufficient heat-production and subnormal temperature.

"6. A wasting of the body-tissues (in relation to the more rapid failure of nutrition of the central nervous system).

"7. A probable compensatory polypnœa, or attacks of dyspnœa (the peripheral indication of the failure of the nerve-centers to assimilate oxygen).

"8. A rapid progress toward death. Future research must negative or confirm these statements."

All the phenomena considered by Andriezen as "predicable results of the ablation or destruction of the gland" are ascribed to the organ as a whole, irrespective of any influence

of the thyroid, which he associates with the respiratory function, and, of course, irrespective also of any connection with the adrenals.

THE ANTERIOR PITUITARY BODY AS THE ADRENAL CENTER.

Hirschfeld,[50] referring to nervous connections of the pituitary, states that a number of anatomists classify this organ among the sympathetic ganglia; then adds: "I am all the more inclined to adopt the latter opinion since I have always seen, in my dissections, *a great number of nerve-fibers extend from the superior cervical ganglia to this organ.*" Unfortunately, no reference is made to the exact distribution of these fibers, but we are fully compensated by an admirable histological study of both lobes of the pituitary by H. J. Berkley,[51] in which he says, referring to the *anterior* lobe: "Nerves, *other than* those belonging to the sympathetic system, are not found."

The nervous supply of the anterior pituitary lobe consists of very fine fibers with numerous ramifications and branchlets, and of bundles of small nerves that follow the course of the arteries. From these originate single fibers which are distributed upon the coils of the epithelial cells, forming the follicles, their ends breaking up in this location into numerous terminal fibers with ball-shaped endings. The follicles referred to, according to Guépin,[52] average less than $^1/_2$ millimeter in diameter (300 to 600 microns). Though often termed acini,—*i.e.*, glands,—they are, in reality, *closed cavities*, alveoli, or vesicles, enveloped in a rich capillary net-work supported by a sparse frame-work of connective tissue. The capillaries of the lobe are made up of a single *endothelial* coat. The alveoli themselves are built of two kinds of *epithelial* cells, the one containing a *large* nucleus surrounded by a relatively clear, though granular, cytoplasm, the other containing a similar nucleus, but buried in a coarsely granular cytoplasm. The arteries reach the organ by way of the infundibulum, and are distributed to the alveoli without at any time penetrating

[50] Hirschfeld: "Système Nerveux et Organes des Sens de l'Homme," Paris, 1866.

[51] H. J. Berkley: Brain, Winter, 1894.

[52] Guépin: Tribune Médicale, Dec. 10, 1891.

them, while the veins return by the same path as the arteries. The partition between the two lobes contains, according to Müller,[53] a net-work of lymphatics lined with ciliated epithelium.

The predominating feature of these anatomical relations is, of course, the connection with the sympathetic system, which suggests that the anterior lobe may prove to be the suprarenal center to which we have so frequently referred. Indeed, we have had abundant evidence of the limited control or influence the bulb and cord have over the adrenals, while the experiments of Vassale and Sacchi have shown that removal of the pituitary gives rise to symptoms of total suprarenal insufficiency. Were the anterior lobe the seat of this all-important function, however, it would necessarily lose its identity as a secreting organ, since its rôle would be to generate, under the influence of a stimulus—toxic blood, for instance—an impulse or impulses that the sympathetic nerves would transmit to the adrenals. The large nuclei of the epithelial cells, the wealth of endothelial and epithelial elements, and the remarkable vascular supply of this lobe, all seem to lend weight to this hypothesis.

As we will see in the chapter on "Immunity," all such protoplasmic elements are endowed with immunizing attributes. Either as stationary phagocytes or alexocytes they are able to react aggressively against various pathogenic elements. That this denotes a latent power in each cell to exert chemotactic influence is generally recognized. But Buchner has shown that leucocytes are not only chemotactic to bacteria, their powerful toxins and bacterial proteids, but also to various substances, down to so inert a material as wheat-flour. This affords evidence that the cellular elements of which the vascular and alveolar structures are composed are endowed with *latent* energy, which, in the presence of any one of a large number of substances, may become *active*. That in so important an organ as the pituitary now seems to be this reserve of energy should be unusual is apparent; we have testimony that such is the case in the anterior lobe in the large size of the

[53] Müller: Jenaische Zeitschrift, Bd. vi, 1891.

nuclei of its epithelial cells. Indeed, if a cell is so divided that its nucleus will remain in one part, the other, composed entirely of protoplasm, will die; but if the latter contain a fraction of the nucleus, it will continue to live: evidence that it is in the nucleus that the main source of energy resides, though it cannot itself live without protoplasm. Whatever interpretation we may give "physiological functions," we are invariably dealing with manifestations of chemical energy. Indeed, we have in organic structures ample evidence to show that during metabolism this chemical energy may become latent or potential mechanical energy, which in turn may pass into vital energy. The seed-pods of certain plants exemplify this admirably: The chemical energy underlying their growth accumulates as latent mechanical energy, and if the pod is merely touched this energy suddenly passes into one connected with the plant's own physiological functions: it explodes and scatters its seeds in every direction.

When these elementary biophysical facts are considered as features of the intrinsic functions of the anterior lobe, it becomes apparent that its dense array of nucleated cells, its endothelial capillary walls, etc., may, with justice, be considered fit constituents for a powerful energy-storing center. The protoplasmic and cellular elements massed in this lobe are now known, through the labors of Metschnikoff, Pfeiffer, Buchner, and others, to react everywhere else in the organism in the presence of a multitude of different toxic agencies: a process doubtless referable to the one property of the protoplasmic cell, formerly recognized as "irritability." If toxic blood, coursing through endothelial walls elsewhere in the body, can excite a protective reaction, it must certainly be able to do so in an organ in which endothelial and epithelial cells and their nuclei are so densely crowded together. If the anterior lobe of the pituitary is really the suprarenal center, the *intensity* of the reaction that any toxic in the blood might excite in the center would regulate the violence of the symptomatic phenomena engendered. We have seen, when studying the adrenals, that poisons cause reactions in these organs that vary in their intensity proportionally with the violence of the toxic energy of these poisons and the dose introduced into the blood-stream.

That the anterior lobe of the pituitary and the adrenals are directly connected, the former constituting the center of the latter, is further sustained by the fact that both organs are united *solely* by sympathetic structures. Thus, while Berkley, referring to this lobe, says, "nerves, other than those belonging to the sympathetic system, are not found,"—confirming *de visu* what other anatomists, among which are Tiedmann, Pourfour de Pettit, Fontana Bok, Hirschfeld, and Bourgery, had been led to surmise,—Dogiel,[54] alluding to the nerve-elements of the adrenals, says: "There are, in the medullary substance, glandular and nerve-cells; . . . the nerve-cells in no way differ from those of any sympathetic ganglion": a conclusion as to the system involved which Cybulski, Biedl, Dreyer, and others have sustained by experimental investigations.

Again, we have seen that Hirschfeld *always* found a large number of fibers to connect the cervical sympathetic ganglia with the pituitary. Berkley states, referring to the anterior lobe: "All nerves belonging to it appear to be derived from branches of the carotid sympathetic plexus." As this plexus is made up of filaments from the superior cervical ganglion on each side, the latter observation confirms the former. We thus have undeniable evidence of a structural connection between the anterior lobe and the sympathetic system. The directness of the path that an impulse starting from this lobe could follow to reach the suprarenal glands—*i.e.*, through the chain of sympathetic ganglia on each side of the vertebral column down to the splanchnic nerves, and through them to the solar plexus, the source of the suprarenal plexus—also points to the anterior pituitary body as the suprarenal center. This is clearly indicated in the annexed colored plate, which shows the course of the nervous tract. The entire adrenal system is colored yellow.

The prevailing doctrine as to the source of the functions of the sympathetic is well illustrated by M. Duval[55] when he says: "It is now recognized that most of the nervous phenomena of the visceral functions have the spinal cord for their center, and that even for its vasomotor functions the sympa-

[54] Dogiel: Archiv für Anatomie u. Physiologie, p. 90, 1894.
[55] M. Duval: *Loc. cit.*

NERVOUS PATH FROM THE ANTERIOR PITUITARY BODY TO THE ADRENALS. *[Sajous.]*

A, Anterior Pituitary Body. 1, Thyroid Gland. 2, Superior Cervical Ganglion. 3, Thoracic Ganglia. 4, Greater Splanchnic Nerve. 5, Lesser Splanchnic Nerve. 6, Solar Plexus. 7, Suprarenal Plexus. 8, Right Adrenal. B, Posterior Pituitary Body, the Governing Center of the Anterior Pituitary Body's Nervous Supply, and General Center of the Cerebro-spinal System.

Vascular Supply of the Adrenals: 9, Suprarenal Vein. 10, Suprarenal Arteries.

thetic nerve utilizes only borrowed power originating in the upper portion of the spinal axis; the case is the same in respect to its influence upon the heart, and also with most visceral reflexes, the centers of which are in the cord; so that even the expression 'sympathetic system' to-day means nothing."

If the pituitary's anterior lobe *is* the nervous center of the adrenals, the confusion in our ideas of the functions of this system are easily explained, since many phenomena ascribed to it have the adrenals as their source. The latter organs fulfilling their functions through a secretion, a further cause of confusion must have insinuated itself in all the experimental work connected with the sympathetic, so that the latter has, in reality, never appeared in its true light. Relieved, however, of all the elements of conflicting testimony which the adrenals involve, its true rôle in the organism cannot but soon be ascertained. Indeed, the system of which the pituitary body seems to be the center would constitute with the adrenals an absolutely autonomous one. This will appear among the data now to be submitted, which indicate that a direct connection exists between these two organs.

As is well known, response is not as prompt when the cut ends of some sympathetic nerves—the splanchnic, for instance —are electrically stimulated, as when the cerebro-spinal nerves are treated in the same manner. When the splanchnic nerve is thus stimulated, several seconds elapse before a slow contraction of the intestines—*i.e.*, of their muscular coat—begins, and this continues some time after the stimulation ceases: evidence that we are dealing with something more than a nervous impulse and with an indirect effect. This recalls experiments to which we have already referred and which now explain this anomaly. Dreyer[56] observed that the effects of the suprarenal blood-raising constituent were increased after stimulation of the splanchnic. Biedl[57] also noted that when the *suprarenal* branches of the splanchnic nerve were cut below the diaphragm, and the lower fragment was stimulated, injections of blood that flowed from the adrenal veins into animals brought on the characteristic phenomena. That the indirect

[56] Dreyer: American Journal of Physiology, Jan. 18, 1899.
[57] Biedl: Pflüger's Archiv, Bd. lvii, H. 9 and 10, 1897.

effects on the muscular coat of the intestines is the result of suprarenal overactivity induced by the current seems clear. But these experimental data simultaneously show, since the great splanchnic nerve includes branches from the fifth thoracic ganglion and filaments which have been traced up to the first ganglion, that the impulses to the adrenals were transmitted from the upper thoracic region.

That the cervical ganglionic chain should be the normal continuation upward seems obvious. Yet, the spinal and cervical nerves, which likewise connect the portion of the sympathetic above the ganglion from which the first branch of the greater splanchnic is given off, with the cord, must also be taken into account; otherwise the impulses might be thought to originate in the latter. Section of the sympathetic system in the neck, therefore, will alone demonstrate whether it is totally independent of the medulla before the pituitary lobe is reached.

Jaboulay's[58] operation for exophthalmic goiter, in which this procedure is resorted to, is instructive in this connection. In his first case section of the nerve on one side at once caused cessation not only of the excessive heart-action and of the exophthalmos, but also of the trembling. But recurrence took place within a few weeks. That such should be the case seems normal if the pituitary plays a prominent part in the disease, since the only result of the operation was to reduce the excessive activity of one of the adrenals while the still overactive pituitary could throw the brunt of its stimulating energy upon the remaining one. In a case operated by Gayot[59] both nerves were divided below the middle cervical ganglion on the left side, and, above this ganglion, on the right. The exophthalmos completely disappeared on the same day and the cardiac pulsations were markedly reduced.

Since then many operations have been performed with more or less success. Anzilotti,[60] for instance, in eleven cases, in which the superior or middle ganglia were removed, always obtained reduction of the exophthalmos, goiter, and tachycar-

[58] Jaboulay: Lyon Médical, March 22, 1896.
[59] Gayot: Lyon Médical, July 26, 1896.
[60] Anzilotti: La clinica moderna, No. 7, 1898.

dia, with cure in some instances. Jaboulay,[61] in a subsequent paper, referred to eleven personal operations, and had reached the conclusion that removal of the superior cervical ganglion gave the best results. As the upper ganglion is the origin of the carotid plexus, we have again reached the anterior pituitary.

Some phases of the question, however, still require elucidation. Why, for example, do the patients not succumb when the bilateral operation is performed? It would seem, if the anterior pituitary is the center of the suprarenal glands, as if these organs should cease to functionate. Analysis of a series of 61 cases, including 45 of epilepsy, 7 of glaucoma, and 8 of exophthalmic goiter, reported by Jonnesco,[62] suggests a solution which coincides with deductions previously referred to in this work. Idiopathic epilepsy, we have seen, is mainly due to accumulation in the organism of toxic products of metabolism, which give rise to sudden exacerbations of suprarenal activity. To sever the connection between the two overactive organs must evidently reduce the morbid phenomena witnessed. Jonnesco, out of the 45 cases above mentioned, "carefully followed" the subsequent history of 19; of the rest, 6 died, while the others were either too recent or had passed from observation. Of the 19 cases, he says that "10 are cured: that is, no spasms have occurred for two years in 5 cases, for nineteen months in 1 case, for eighteen to fifteen months in 3 cases, and for six months in 1 case." He then adds: "6 of those upon whom I have operated are decidedly improved; 2 absolutely unchanged. To sum up, 55 per cent. of the operations resulted in cure, 28 per cent. in improvement, and 15 per cent. were without effect."[63] We thus have evidence that a fair proportion of cases may be benefited by the operation.

There is another side to this question, however. None of the cases mentioned were operated before August, 1896, from which month Jonnesco starts his series of 61 cases. The paper in Medicine having been published in August, 1899, all the

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[61] Jaboulay: Presse Médicale, Feb. 22, 1898.

[62] Jonnesco: Medicine, August, 1899.

[63] Given *verbatim* as translated by Dr. Willard Bartlett for Medicine, August, 1899.

operations referred to, including those in epileptics, must have been performed within three years. If the history of these epileptics is studied from our standpoint, the 6 patients who died "either in epileptic attacks or as a result of an intercurrent disease" are to be included in the series "carefully followed," and we have as a result, 25 cases which, *within three years*, showed a mortality of 24 per cent. In other words, nearly one-fourth of the cases operated succumbed within that time, and, as all the operations were not performed during the earlier months of the three years, it stands to reason that some of the 6 must have died within a shorter time subsequent to the surgical procedures. This in no way reflects upon Jonnesco's records, since he only refers, in keeping with the present custom in this particular, to the immediate effects of the operation, while *we* are studying remote results from a *new* standpoint. Why this great mortality?

Can we conclude that, in every series of 25 unoperated cases of epilepsy, 6 die "in epileptic attacks or as a result of an intercurrent disease" within such a short period, and say, with Jonnesco, when referring to the remote effects of bilateral resection of sympathetic ganglia, "there are none"? He can legitimately say this, referring, as he does, to the trophic psychical and general well-being of the patient immediately after the operation; but, as is well known, such a mortality does not attend idiopathic epilepsy. Although the occurrence of death during attacks cannot be said to be rare, it is too infrequently observed to enable us to ascribe the lethal results over and above the usual ratio to this cause. Evidently the operation must exert some morbid influence in the after-history of cases in which it is performed.

This is further emphasized by the statistics of 37 operated cases collected by G. Marchant,[64] including 7 of his own. The series showed 8 deaths: 5 immediate and 3 remote. Three of the former are ascribed to "grippal pneumonia" or "pulmonary congestion," the fourth to "erysipelas," and the fifth occurred in a chronic drunkard, who died on the third day after showing "extreme agitation." Two of the "remote" cases died

[64] G. Marchant: Semaine Médicale, Nov. 2, 1898.

within six weeks, and the third from chronic nephritis eighteen months after the operation. In one of Jaboulay's cases death occurred the sixth day; the necropsy also revealed congestion of the base of the right lung. Peugniez[65] also obtained most satisfactory results, with every evidence of a permanent and final cure, but a few weeks later the state of the patient became rapidly worse, and death soon followed.

In the light of the views advanced in the present work, not only are the beneficial results obtained accounted for, but the cause of the unusual mortality also becomes clear. Jonnesco's deaths during epileptic paroxysms obviously point to a further increase of toxic waste-products: *i.e.*, to their incomplete oxidation through the aggravated suprarenal insufficiency caused by dissociation of the adrenals from their overactive center. This very dissociation, on the other hand, in cases possessed of less vulnerable adrenals, or of a less active pituitary, accounts for the reduction of the abnormal suprarenal activity to a normal level: a feature which also obtains in the other disorders in which the operation has been employed. We have excessive suprarenal activity in exophthalmic goiter, for example, and *if* the operation does not reduce this activity *below* the normal, a result that greatly depends on the condition of the adrenals themselves, a marked and perhaps lasting improvement *as regards the disease itself* may occur.

But the deaths during epileptic seizures, and the unusual post-operative mortality due to intercurrent disorders, point to a *subsequent* reduction of suprarenal efficiency and perhaps to acquired vulnerability to the morbid effects of toxic agencies, as a result of the operation. The "intercurrent acute diseases" referred to in Jonnesco's paper are not enumerated: a fact suggesting variety and showing that no special disease (such as "ether-pneumonia" occasionally observed when this anæsthetic is employed) follows section or resection of the sympathetic nerves. In the fatal cases referred to by Marchant, Jaboulay, and Peugniez, grippal pneumonia, erysipelas, and chronic nephritis appear as lethal maladies. These, added to epilepsy, not only indicate the wide range of morbid conditions that may

[65] Peugniez: Gazette Médicale de Picardie, Nov., 1898.

ensue, but they distinctly point to the fact that the entire list of conditions collectively considered under the term "intoxications" of intrinsic or extrinsic origin is brought into action. Indeed, there seems to be no line drawn, no particular morbid field common to these operated cases except the one vast source of suprarenal insufficiency represented by poisons in general, bacteria and their toxins, toxic products of metabolism, etc.

The operation brings the cardiac action down to a remarkable degree—10 pulsations in a case reported by Combemale and Gaudier.[66] Berry,[67] in a review of the literature of the subject, refers to a case in which the patient died a few hours after operation after having shown an "extremely rapid pulse." That we are dealing with weakened and finally overpowered suprarenal glands in post-operative cases is not only suggested by the class of disorders witnessed, but it is also shown post-mortem by the pulmonary congestive phenomena referred to: a normal result of the vasodilation which marked reduction or arrest of the suprarenal secretion entails.

The few other general affections in which sympathectomy has been resorted to are all, if the views advanced in this work are exact, expressions of excessive suprarenal activity. Exophthalmic goiter, therefore, can serve as a type to illustrate the course of events when the suprarenal glands are not able, through inherent or acquired debility, to continue their functions when separated from their center, the anterior pituitary body. Peugniez's case of this disease, in which sympathectomy was performed on both sides, being one of this kind, it can serve as example. The patient, a girl 20 years of age, presented the typical signs: goiter, exophthalmos, tachycardia, and exceedingly profuse sweating. The operation on the left side was performed on October 28th; that on the right on November 20th. Less than two weeks after the *latter* operation the goiter had completely disappeared; exophthalmos had become greatly reduced; the pulse likewise; and the sweating had ceased. The patient left the hospital on December 12th in a

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[66] Combemale and Gaudier: Gazette Hebdom. de Médecine et de Chirurgie, April 24, 1898.

[67] Berry: Trans. Edinburgh Medico-Chirurgical Society, Jan. 17, 1900.

most satisfactory condition, with every probability of a prompt and final recovery. On January 4th—*i.e., three weeks later*—Professor Peugniez, having visited her, was shocked at her appearance. A few days had sufficed to bring her to the last degree of emaciation; the lids were wide apart, so great was the exophthalmos, and pus exuded from the conjunctival recesses. "Galloping cachexia" supervened, soon ending in death.

If all these facts are collectively considered, they not only show that a direct functional communication exists between the anterior pituitary body and the adrenals through the cervico-thoracic ganglionic chain of the sympathetic system, its greater splanchnic nerve, and the semilunar ganglia, but that the system thus formed is an autonomous one, of which the suprarenal secretion in more or less great quantities is the primary functional result.

The existence of such a system and its true importance are further emphasized when the direct connection between the adrenals and cardiac action is further analyzed. On the other hand, the cause of the baneful effects of resection of the sympathetic ganglia, and particularly its influence upon the rapidity of the heart-beats, become apparent when we realize that the heart primarily owes its activity to the secretion of the adrenals. That cases survive the operation at all is due to direct spino-adrenal nerve-paths, survivals of the earlier days of life, as will be shown.

We have seen that when Schäfer and Oliver injected suprarenal extract intravenously a great increase in cardiac and respiratory activity was noticed. Was this due to a local effect upon the heart itself or to an action upon the cardiac nerve-centers? The marked effect of suprarenal extract on muscular tissue indicates that the heart itself must have been stimulated. As previously shown, detached pieces of vascular walls completely disconnected from their nerve-centers undergo contraction when suprarenal extract is applied to them. Even dried tissues, as observed by Oliver,[68] respond to its action. After using other extracts with little or no effect the latter investigator says: "The suprarenal extract invariably produced the

[68] Oliver: Journal of Physiology, Nos. 4 and 5, March 12, 1897.

most decisive contractions, and one, moreover, which persisted 30 to 60 minutes."

As to a direct action upon the heart during life, we will recall the experiments of Biedl, who found that when, in test animals, removal of the entire cord had brought the blood-pressure down to almost nothing, the heart would respond with vigor to injections of suprarenal extract, the pressure rising to 160 millimeters mercury. Oliver conducted similar experiments, and, referring to vascular pressure, says: "The constriction was equally pronounced whether the spinal cord remained intact or was destroyed." We have conclusive testimony in these facts to the effect that, if the cardiac tissues themselves were to receive, during life, an injected dose of suprarenal extract, they would instantly respond to its effects.

The topographical anatomy of the structures between the adrenals and the lungs, and a review of facts previously recorded in this work, show how this is accomplished. The suprarenal secretion, we have seen, reaches the inferior vena cava—directly on the right side, and through the renal or phrenic vein on the left. It is, therefore, poured into blood collected from the kidneys, the pelvic organs, the lower extremities, etc., and deprived of the oxygen appropriated by these structures. While venous blood, even in the right ventricle, still contains oxygen, this gas is held by the hæmoglobin of the corpuscles; so that the plasma itself contains none. But we have previously seen that various investigators—Cybulski, Biedl, Dreyer, among others—have found secretory products in blood received from the adrenals destined for the inferior vena cava. These two facts—*i.e.*, the absence of oxygen and the presence of suprarenal secretion in the latter vessel—can lead to but one deduction: *i.e.*, that *the suprarenal secretion reaches the right ventricle in its primary state*, or at least very slightly modified in composition.[69] The important rôle it must fulfill here becomes evi-

[69] We say "slightly modified composition" because we have reason to believe that the venous blood of the inferior vena cava above the level of the adrenals and up to the pulmonary air-cells is the seat of a special protective process, in which the marked reducing power of the suprarenal secretion acts as a dissociating agency. There is obviously no literature on this subject, and as this work is to contain nothing that cannot be poised on experimental data, a mere mention must suffice.—S.

dent when we realize how rapidly the cardiac functions are impaired as soon as a violent toxic has brought on suprarenal insufficiency: the source, we now know, of the phenomena that portend a fatal issue.

Schmiedeberg, we have seen, found that the cardiac arrest brought on by digitalis was "not of the nature of a paralysis, but of a spasm"; that the brunt of the action of this drug is exercised upon the right heart has been observed by several able clinicians, Germain Sée among them. The meaning of this fact is obvious: digitalis is probably the most perfect cardiac stimulant of our pharmacopœia, but only because better than any drug it enhances the activity of the anterior pituitary body, which, in turn, so stimulates the suprarenal glands as to bring them to their highest functional possibilities. The unusual amount of its secretion, dissolved in the plasma, reaches the cardiac cavity, and there produces what experimental physiology has shown it to always cause in muscular tissues: *i.e., contraction.*

A review of known facts concerning the effects of digitalis on the heart shows the active part played by the adrenals in the phenomena witnessed. A large dose, one capable of bringing on marked suprarenal overactivity, occasions an enormous rise of vascular pressure. Wood says that the arterioles of a frog's web or of the mesentery of a rabbit undergo such marked contraction that their lumen is almost obliterated. The cardiac systole is "abnormally strong," the ventricles becoming white when the blood is being forced out. Germain Sée, von Openchowski, and others have emphasized the fact that this action is greatest on the right side of the heart. The pulse is at first slowed, strengthened, and hardened; then becomes dicrotic: a suggestive fact,—a primary warning, perhaps. At this time, indeed, the stage of suprarenal insufficiency may suddenly appear,—*i.e.*, the supposed "cumulative" stage,—and death occur—the result of exhaustion of the suprarenal center, with arrest of the heart in diastole. If this does not occur at once, "ventricles and auricles no longer beat together"; one portion of the heart is dilated while the other contracts. Wood[70] says, in this connection: "In the last period of the poi-

[70] Wood: *Loc. cit.*

soning the auriculo-ventricular arhythmia grows more pronounced, and finally the cardiac contractions become entirely irregular, until at last there is that condition which is sometimes spoken of as *delirium cordis.*" But why this arhythmia after the stage of *insufficiency* has begun? That the previously overworked right ventricle had been the first to collapse—in diastole—is evident.

It seems to us that all these facts warrant the deduction that *the suprarenal secretion, mixed with the blood-plasma, reaches the right ventricle in its primary state, and serves mainly to increase its propulsive power in order to insure adequate distribution of the blood in the lungs.*[71]

If the anterior pituitary body is the functional center of the adrenals, exophthalmic goiter, due to overstimulation of the former organ by an excess of thyroid secretion, should show symptoms corresponding to those of digitalis, since we have said that the adrenals were the mechanical source of these symptoms. Again, as we have also stated that some of the symptoms ascribed to the sympathetic system are of suprarenal origin, both digitalis poisoning and exophthalmic goiter should include in their symptomatology some signs usually attributed to the sympathetic system. Any other drug might be selected for the purpose, but digitalis alone approaches thyroid extract in its power to stimulate the organs in question.

Exophthalmic goiter being a chronic disease, while the symptoms of digitalis poisoning given are those of an acute condition (the erethic stage being only referred to, since the cachectic stage does not typify *activity* of the organs), the comparison is evidently in no way calculated to favor our argument. But even then, and leaving out only symptoms essentially associated with chronicity, a common anatomical source is easily traceable for many phenomena, notwithstanding the dissimilar pathogenic agencies to which the two morbid states owe their existence. In both, for example, excessive cerebral hyperæmia and oxidation are manifested by violent headache, excitability, insomnia, hallucinations, etc. The muscular

[71] Weakness of the right ventricle as a result of suprarenal insufficiency is an important factor in the pathogenesis of pulmonary phthisis; its various phases will be discussed when this disease is studied.—S.

twitchings of exophthalmic goiter are represented in digitalis poisoning by painful contractions. In both appear the essentially "sympathetic" or "vasomotor" phenomena, superficial heat and flushings, dyspnœa, and suffocation. Even exophthalmos is duplicated in digitalis poisoning. While prominence of the eyeballs is witnessed in most grave cases, Wood[72] says: "More or less exophthalmos is said to have persisted for weeks in some cases." Strychnine, atropine, alcohol, opium, quinine, and a few other agents more or less actively reproduce these and other signs of exophthalmic goiter when administered in suitable doses. But none of these give rise to cardiac symptoms similar to those of digitalis, because none possess its power to *safely* stimulate the anterior pituitary lobe to the same extent. They induce exhaustion of its cellular elements before its maximum resources have been utilized: *i.e.*, they paralyze it in the midst of its functions—the underlying cause of suprarenal insufficiency.

If we now group all these facts, it will become apparent that seemingly irrelevant data introduced merit the title of confirmatory evidence. To demonstrate that the anterior pituitary body was the functional center of the adrenals a *direct* relationship had to be shown to exist between them. We ascertained that this direct connection was established through sympathetic ganglia and splanchnic nerves. It then became necessary to isolate the bulbo-spinal center as direct causal factor in the production of certain phenomena belonging to the pituitero-suprarenal domain. This was done by demonstrating that structures previously shown to be governed by the anterior pituitary—*i.e.*, the adrenals—could, through their secretion, fully sustain cardio-vascular action when all spinal connections had been severed. The aim was not, however, to show that the bulbar centers were deprived of all influence over the adrenals,—since we do not, as yet, know whether this is the case or not,—but that some of the major functions ascribed indirectly or directly to the bulb—cardiac action, respiration, muscular activity, etc.—were primarily related to the newer system referred to. This was also suggested by the fact that,

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[72] Wood: *Loc. cit.*, p. 310.

while the functions of the adrenals gradually ceased after their isolation from the bulbo-spinal centers, cardio-vascular action could be very actively maintained by injections of suprarenal extract: a result which, as shown by the experiments of le Gallois, Goltz, Stricker, and Ustimowitch, could not be reached by other means.

The all-important *direct* action of the suprarenal secretion on the heart was then introduced to further strengthen the relationship between the anterior pituitary and the adrenals, previously found to exist through the intermediary of sympathetic structures. The function of the anterior pituitary body then affirmed itself, since the active symptoms of digitalis were found to include not only phenomena directly assignable to inordinate suprarenal secretion, but others which experimental physiology—including the experiments quoted herein—had ascribed to bulbar influence. To finally confirm all these facts, a *chronic* disease, previously shown to be due to excessive stimulation of the anterior pituitary body, was compared symptomatically with acute digitalis poisoning, to ascertain whether two conditions, so remote pathogenically according to our present knowledge, could also show signs of kinship. We have seen that even this severe test did not fail to point to a common origin, the anterior pituitary body, for many of the cardinal phenomena witnessed in both.

If to all this we now add the results of de Cyon's experiments in horses, dogs, rabbits, and guinea-pigs, in which he noted that the least pressure upon or electrical stimulation of the pituitary caused sudden variations of vascular pressure and of cardiac action precisely coinciding with the effects now so often shown in this work to be those of suprarenal overactivity, and also the fact that acromegaly, essentially a disease of the anterior pituitary body, likewise presents this kinship with the adrenals, including the "erethic" and "cachectic" stages, and various vasomotor phenomena, the following deductions seem warranted:—

1. The thyroid gland supplies the blood with a secretion which has for its object to sustain the functional activity of the anterior pituitary body.

2. The anterior pituitary body is directly connected with the

adrenals through the cervico-thoracic ganglia, the splanchnic nerves, and the semilunar ganglia of the sympathetic nervous system.

3. The thyroid gland, the anterior pituitary body, and the adrenals are functionally interdependent, and constitute a system through which cardiac action, respiration, and general cellular oxidation are maintained.

4. The thyroid gland sustains the normal functional activity of the anterior pituitary body, while the latter in turn maintains the normal activity of the adrenals.

5. The functional activity of the anterior pituitary body is increased when the blood contains an excess of thyroid secretion or sufficiently-active toxics: bacterial toxins, poisons, physiological toxalbumins, etc., to compromise the general cellular integrity of the organism.

6. The functional activity of the adrenals is increased proportionally with that of the anterior pituitary body when the latter's activity is increased from any cause.

7. The functional activity of the anterior and posterior pituitary bodies is PASSIVELY *decreased when the blood contains an insufficient proportion of thyroid secretion or is inadequately oxygenated, or when from any cause its intrinsic metabolism is reduced or impaired through deficiency of any of its molecular constituents.*

8. The functional activity of the anterior pituitary body is ACTIVELY *decreased when the blood contains a sufficiently active toxic of any kind, bacterial toxin, poison, etc., to induce excessive metabolism of its intrinsic cellular elements and thus cause exhaustion or molecular metamorphosis of the latter.*

9. The functional activity of the adrenals is decreased proportionally with that of the anterior pituitary body whether the reduced activity of the latter be due to active or passive pathogenic factors.

If all the facts so far recited in the present work prevail, another deduction suggests itself regarding the part played in the body by the system thus formed by the anterior pituitary and the adrenals through their connecting nerves (and which we will now term, for the sake of brevity, the "adrenal system"): *i.e.*, that *its primary function is to insure oxidation.*

Again, the fact that its functional activity is increased, with the result that oxidation processes are correspondingly

enhanced when poisons of any kind threaten the integrity of the organism, also indicates that *its secondary function is to protect the organism against disease.*

In other words, the "adrenal system" simultaneously sustains life and aims to preserve it.

CHAPTER VI.

THE ADRENAL SYSTEM AND VASOMOTOR FUNCTIONS.

THE OXIDIZING SUBSTANCE AND THE MOTOR NERVES IN THEIR RELATION TO MUSCULAR CONTRACTION.

Division of the spinal cord below the medulla oblongata is followed by dilation of all the vessels of the organism, while electrical stimulation of the lower cut segment of the cord causes constriction of these blood-vessels and a general rise of blood-pressure. Evidently constriction and dilation of the vessels of the organism are regulated by centers located in the medulla and pons, in accordance with the present teachings. We are, therefore, referred to these centers for the impulse-waves (transmitted through the vasomotor nerves) which govern the structures that co-operate with the adrenal system in the performance of its physiological functions. What is the nature of the relationship between the adrenal system and the vasomotor system?

A cursory analysis of this question soon reveals an important feature, namely: that the voluntary, or skeletal, muscular system cannot be classed with the other organs in respect to vasomotor functions. The sympathetic system is the essential, perhaps the only, source of vasoconstrictor nerves, and yet this system is not known to extend to the extremities. Again, vasoconstrictors and vasodilators are said to accompany the larger nerve-bundles,—the sciatic, for instance; but a survey of the field distinctly shows that the evidence as to the existence of separate vasoconstrictors is purely inferential. Since the sympathetic nerve does not appear to send subdivisions to this class of muscles, the association of constrictors of another source introduces an element of confusion, not only as regards the peripheral structures themselves, but particularly in respect to the central origin of the two systems classed under the one single term of "vasomotors." As it is impossible to

proceed without clearing this question, we will first ascertain whether the prevailing views as to the physiology of the circulation in the muscular system may not, in the light of our own conceptions, be subject to change.

The Oxidizing Substance and Myosinogen. — In the production of muscular contraction a nerve-impulse is of course transmitted to the muscular elements; but how are this impulse and the resulting contraction related to the functions of the blood itself? This question is suggested by the rôle assigned in the foregoing pages to the oxidizing substance.

Stewart[1] refers to the thermal phenomena of muscular contraction as follows: "When a muscle contracts, its temperature rises; the production of heat in it is increased. This is most distinct when the muscle is tetanized, but has also been proved for single contractions. The change of temperature can be detected by a delicate mercury- or air- thermometer; and, indeed, a thermometer thrust among the thigh-muscles of a dog may rise as much as 1° to 2° C. when the muscles are thrown *into tetanus.*" That tetanus is a phenomenon of hyperoxidation through suprarenal overactivity we have repeatedly seen when studying the action of drugs. This affords a first clue: If the plasma contains an oxidizing substance, the chemical changes in muscular tissue during contraction—*i.e.*, absorption of oxygen, increased production of carbon dioxide, change of reaction from neutral or alkaline to acid, and finally the formation of sarcolactic acid—clearly suggest that the contractile process and the mechanical energy utilized may be due to an increased supply of oxygen through the agency of the oxidizing substance. Indeed, Kronecker has shown that "the injection of arterial blood or even of an oxidizing agent like potassium permanganate into the vessels of an exhausted muscle also causes restoration." If an agency so remote in composition from the normal organic fluids can restore merely through its oxidizing power an exhausted muscle, so eminently physiological a fluid as the blood-plasma, charged with oxygen *in loose combination,* must surely possess correspondingly active properties. Indeed, the link seems to

[1] Stewart: "Manual of Physiology," p. 598.

be a strong one if the full meaning of the following sentence from Foster's "Physiology" (sixth edition) is gathered: "We might compare a living muscle to a number of fine, transparent, membranous tubes *containing blood-plasma.*" If we also recall the fact that capillaries do not possess contractile fibers and that arterioles represent the ultimate subdivision to which vasomotor nerves are distributed, it becomes clear that we have all the mechanical elements necessary to account for some unexplained phenomena that attend muscular contraction. An impulse capable of causing a change of caliber of a peripheral arteriole would thus suddenly admit more arterial blood—*i.e.*, more oxygen-laden plasma—into the "fine, transparent, membranous tubes," and contraction, an inherent property of muscular tissue, would follow.

The prevailing views as to the nature of the process through which the mechanical energy utilized during muscular activity cause contraction or retraction may be illustrated by selections from Professor Foster's text. Referring to the chemical analogy between the axis-cylinder and muscle-tissue, he says: "We have no satisfactory evidence that in a nerve even repeated nervous impulses can give rise to an acid reaction" . . . "nor have we satisfactory evidence that the progress of a nervous impulse is accompanied by any setting free of energy in the form of heat." In the summary, referring to the terminal phenomena, he remarks: "This muscle-impulse, of which we know hardly more than that it is marked by a current of action, travels from each end-plate in both directions to the end of the fiber, where it appears to be lost; at all events, we do not know what becomes of it. As this impulse-wave, whose development takes place entirely within the latent period, leaves the end-plate, it is *followed* by an explosive decomposition of material, leading to a discharge of carbonic acid, to the appearance of some substance or substances with an acid reaction, and probably of other unknown things, with a considerable development of heat. This explosive decomposition gives rise to the visible contraction-wave, which travels behind the invisible muscle-impulse at about the same rate, but with a vastly increased wave-length. The fiber, as the wave passes over it, swells and shortens, and thus brings its two

ends nearer together. When repeated shocks are given, wave follows wave of nervous impulse, muscle-impulse, and visible contraction; but the last do not keep distinct; they are fused into the continued shortening which we call tetanus."

The last word, "tetanus," stands as the highest expression of a rapid succession of nervous impulses; but, viewed from our standpoint, this succession of impulses can as readily produce successive variations of vascular caliber, and give rise to precisely the phenomena witnessed, by admitting the oxidizing substance of the blood-plasma into the fine, "membranous tubes." The shock experienced when the current is turned "on" or "off" further suggests that the latter process is the true one. "The mere passage of a constant current of uniform intensity through a nerve does not, under any circumstances," says Professor Foster, "act as a stimulus generating a nervous impulse; such an impulse is only set up when the current either falls into or is shut off from the nerve. It is the *entrance* or the *exit* of the current, and not the continuance of the current, which is the stimulus." . . . "It is the sudden change from one condition to another, and not the condition itself, which causes the nervous impulse."[2]

The confusion that attends prevailing views as to the manner in which muscular tissue is physiologically caused to contract is readily accounted for when, in the light of the newer conceptions outlined in the last chapter, we analytically dissociate the various causal elements of muscular activity. Indeed, we have seen that various phenomena ascribed to the sympathetic system belonged to the domain of the suprarenal glands, *i.e.*, to the newer system described; we are again brought to realize that in all organs certain functions must likewise, and for the same reasons, be disconnected from others as regards their immediate purpose in the tissues. Thus, the fact that the muscle-*impulse*, which "travels from each end-plate in both directions to the end of the fiber, where it appears to be lost," is at present considered as an inherent, though causal, element of the "explosive decomposition of material, etc.," through its activity as a physiological stimulus.

[2] All italics are our own.

But if we can separate these elements of the process into two distinct parts, viz.: (1) a nervous impulse to the muscular elements themselves, and (2) a simultaneous change in the caliber of the local arterioles, the fact that as the impulse leaves the end-plate "it is followed by an explosive decomposition of material, leading a discharge of carbonic acid," will stand as the only result to be expected. Such a division becomes necessary in the light of our conception of the process.

While the nerve-impulses only have for their purpose to excite and govern the function, the blood—*i.e.*, the blood-plasma mainly—through its oxidizing substance becomes the factor through which the chemical process to which contractile work is due is suddenly awakened. A feature of this conception upon which particular stress must be laid—since it applies to all organs—is that it dissociates from the oxidation process *per se* a stimulus which does not belong to it and which, therefore, introduces elements of confusion. "We cannot tell," says Stewart, "in what the 'natural' or 'physiological' stimulus to muscular contraction in the intact body really consists, nor how it differs from artificial stimuli." Relieved of this autonomous agency, the organic physico-chemical processes enter within the limits of exact investigation.

Oxygen in other fields of thermochemistry is known to constitute the reactionary agent through which "explosive decomposition" is awakened and sustained. That it fulfills the same rôle in this connection, some complex organic compound in the muscular fibers constituting the primary source of energy or fuel, is probable. Under these circumstances the passive "irritability" of a living muscle would be maintained by a continuous reaction in which the reagents would be these compounds—*i.e.*, hydrocarbons—and the oxygen held in loose combination in the blood, particularly the blood-plasma, which penetrates the contractile elements themselves. This *irritability* would then become abruptly converted into *contractility* when the blood-supply—*i.e.*, the plasma in the contractile fibers—would be increased through the arrival of more oxygen.

Considerable familiar evidence besides that already adduced is available in support of this conception of the general physiology of muscle-tissue. Although continuous muscular

contractility is generally thought to be associated with nerve-impulse, destruction of all nervous connection with a muscle does not cause it to lose its excitability. Its inherent property in this particular is shown by the fact that, although the apex of the heart contains no nerve or nerve-cells, it nevertheless responds to stimulation. Even when detached from the body, muscles preserve their contractility for a time under suitable conditions. This would appear to eliminate the need of further energy to account for the phenomena witnessed; but the contrary is the case, since it shows why muscular tissue, owing to its inherent irritability, responds to various stimuli: vital, electrical, physico-chemical, and mechanical. Electricity, we know, acts as a powerful stimulus, but heat alone acts in precisely the same manner if the temperature is adequate and is raised rapidly; marked contraction may thus be caused when 30° C. is reached, and violent activity induced before the muscle is heated to 45 degrees. Chemical stimuli will produce the same effect, provided the reaction induced occurs with sufficient rapidity.

That the nervous impulse is not the source of mechanical energy utilized under these circumstances, is shown by the fact that a chemical stimulus applied to a nerve, ammonia, for instance, will not stimulate it though it will excite the muscle; various acids, hydrochloric, acetic, etc., will give rise to the same phenomena. "Certain poisons (curare) cause the motor nerves to become completely incapable of action," says M. Duval, "and, therefore, incapable of transmitting irritation to a muscle; nevertheless, under these circumstances, the excited muscle can directly pass from the state of rest to that of activity (Claude Bernard, Kölliker); the ultimate and fine nervous ramifications that they contain take no part in this *irritability*, since the poisons referred to kill mainly the intra-muscular endings of the nerves (Vulpian). A motor nerve separated from the cerebro-spinal axis loses, after four days, all excitability; the muscle, on the contrary, previously innervated by this nerve remains directly excitable more than three months (Longet)."

That muscle is directly and independently excitable by a large number of stimuli is evident; that oxygen should,

through exacerbations of a continuous physico-chemical reaction of which its tissues are the seat while in the passive state, be able to suddenly awaken the active state is as clear. When the muscle is in the passive state, the transformation of energy incident upon the continuous reaction manifests itself as heat; while, when it is active, it manifests itself as greater heat *plus* mechanical work. Armand Gautier has ascertained that a working muscle took up nine times more blood than a resting one, and that the ratio of carbonic acid given off by it or transmitted to the venous blood was nearly one hundred times greater. This raises the question as to whether the conversion of chemical energy into the mechanical work upon which contraction depends must first be transformed into heat energy. A study of this question by Professor Gautier, based on Carnot's investigations, showed that, just as in a voltaic cell in which the chemical potential at once appears under the form of electricity without passing through the intermediate state of heat, so can intramuscular chemical energy become directly transformed into work. Indeed, he found that 65° C. (149° F.) would represent the final temperature of an active muscle, were it otherwise, and reached the conclusion that "a muscle contracts and works owing to a direct transformation of the chemical potential into elastic tension, without ever requiring the intervention of the heat which theoretically accounts for internal combustions."

These facts seem to us to warrant the deductions:—

1. That the mechanical energy utilized by living voluntary muscles in the passive state is converted chemical energy, the result of a reaction in the muscular contractile elements during which various compounds, mainly hydrocarbons, are oxidized.

2. That active muscular work is the result of an exacerbation of the activity of this mechanical process, attended with a direct transformation of the passive potential: i.e., irritability, into the active potential: i.e., contractility.

The suggestion that the reaction occurs in the living contractile elements themselves cannot, for obvious reasons, be demonstrated experimentally. But if we associate Foster's comparison of a living muscle to "a number of fine, transparent, membranous tubes containing blood-plasma" with our

conception of the nature of blood-plasma as an excipient for an oxidizing agent of adreno-pulmonary origin, on the one side, and, on the other, recall the view of Englemann, that a fluid substance passes from the bright bands of the fiber—*i.e.*, the interstitial disks—into the dark bands—*i.e.*, the contractile disks,—the intimate process would be as follows: *The hydrocarbon compounds would occupy the contractile disks, while the oxidizing substance would fill the interstitial disks, and on the proportion of the latter entering the contractile disks would depend the activity of the oxidation process.*

Further evidence that the general process outlined prevails may be obtained by tracing the identity of myosin: the substance found in the muscles after death. "While dead muscle contains myosin, albumin and other proteids, extractives, and certain insoluble matters, together with gelatinous and other substances not referable to the muscle-substance itself," says Professor Foster, "living muscle *contains no myosin*,[3] but some substance or substances which bear somewhat the same relation to myosin that the antecedents of fibrin do to fibrin, and which give rise to myosin upon the death of the muscle. There are, indeed, reasons for thinking that the myosin arises from the conversion of a *previously existing body which may be called myosinogen*, and that the conversion takes place, or may take place, by the action of a special ferment, the conversion of myosinogen into myosin being very analogous to the conversion of fibrinogen into fibrin. We may, in fact, speak of *rigor mortis* as characterized by a coagulation of the *muscle-plasma* comparable to the coagulation of blood-plasma, but differing from it inasmuch as the product is not fibrin, but myosin. The rigidity, the loss of suppleness, and the diminished translucency appear to be, at all events, largely, though probably not wholly, due to the change from the *fluid plasma* to the *solid myosin*. We might compare a living muscle to a number of fine transparent membranous tubes containing *blood-plasma*. When this blood-plasma entered into the 'jelly' stage of coagulation, the system of tubes would present many of the phenomena of *rigor mortis*. They would lose much of

[3] All italics are our own.

their suppleness and translucency, and acquire a certain amount of rigidity. There is, however, one very marked and important difference between the *rigor mortis* of muscle and the coagulation of blood. Blood during its coagulation undergoes a slight change only in its reaction; but muscle during the onset of *rigor mortis* becomes distinctly acid."

If myosinogen were the precursor of the myosin of *rigor mortis*, what would its composition probably be and how would it become metamorphosed into myosin?

We have submitted the data sustaining our view as to the existence of the oxidizing principle, and have referred to it as a body derived from the suprarenal glands, which, in passing through the lungs, entered into loose combination with oxygen. The labors of Schmiedeberg, Salkowsky, Jaquet, Abelous and Biarnés were quoted to show that such a principle had also been found by chemical methods, though its origin remained unknown to them.

If combustion of products of nuclein metabolism in the blood-plasma, through the presence therein of oxidizing substance, can produce uric acid, it seems reasonable to conclude that, if this same substance is also present in myosinogen, we should find evidence of a similar action. Not only is this the case, but the same products of metabolism are found in muscle-serum: the liquid portion of muscle-plasma obtained by rubbing up and expressing fresh muscle. Though obtained only in very small quantities, the purin bases, creatin, xanthin, hypoxanthin, and creatinin, are always found in addition to their end-product, uric acid. Phosphoric acid—a combustion product accounted for by the presence of the phosphate of potassium—is another link between muscular plasma and that of the general blood-stream. Of course, these various bodies should not be considered as elements of muscular activity. Their history indicates that, along with other albuminoids found, they are mere passive hosts of the muscular plasma as waste-products of muscular *tissue*-metabolism, destined to be converted here, as elsewhere in the organism, into harmless bodies, acids or others.

The active constituents of myosinogen, as far as muscular irritability and contractility are concerned, must be of another

kind, and are perhaps specific to muscle. Especially must this be the case since it possesses, we have seen, a special physical attribute: *i.e.*, the direct conversion of chemical energy into mechanical work, without involving the *corresponding* evolution of heat which oxidation elsewhere in the organism engenders. The word "corresponding" is used because we must not lose sight of the fact that considerable heat is produced during muscular contraction, and, indeed, that it is subject to marked variations under the influence of fatigue, tension, the state of the blood, the work done, etc. Yet the heat evolved is not commensurate with the muscular work done, and if we deduct from the heat potential actually produced that which intramuscular combustion of waste-products incident upon increased exertion entails—an unproductive factor as regards work—the need of the direct conversion of chemical energy into mechanical work—*i.e.*, contraction of the muscle—will appear.

One of the constituents of myosinogen upon which its physical function depends must be glycogen, since it is the constituent of muscle which diminishes during activity, while it accumulates during rest. This body was shown by Claude Bernard in 1848 to be formed in the liver-cells from food, especially from sugars and starches, derived in turn from glucose: one of the products of digestion. Herbivorous animals, such as oxen, horses, etc.,—*i.e.*, those that only feed upon substances that contain these hydrocarbons,—are obviously endowed with great muscular power. It is evident, therefore, that the source of the energy to be ultimately transformed into mechanical work must be stored in these vegetable substances to a very great extent. Glycogen may not, however, migrate as such toward the muscular elements—since it would undergo oxidation in the blood; it is thought to be retransformed into glucose by a ferment and distributed as such to the muscular tissue, where it is again dehydrated ($C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$) into glycogen, ready for functional use. This question will be studied later on.

Outside the organism lactic acid is known to be a product of fermentation of glucose, dextrin, and glycogen; hence the conclusion that *sarco*lactic acid is formed during muscular contraction. According to prevailing views, however, the evidence

tends to show that such is not the case, because sarcolactic acid is produced during progressive *rigor mortis*, precisely as it is during muscular contraction. If, however, the process is interpreted from our standpoint, including the presence of an oxidizing principle in the muscle-plasma,—*i.e.*, the myosinogen, —this negatory evidence is eliminated. According to classic doctrines, the nervous impulse is a *direct* initial factor of muscular contraction, whereas from our standpoint it is an indirect initial factor, oxygen assuming the place now accorded the nerves. The continuation of oxidation during the progress of *rigor mortis*, therefore, becomes a normal outcome of the *post-mortem* vascular dilation, the remaining oxygen entering into combination with the hydrocarbons present, as long as the myosinogen is sufficiently liquid to permit of it: *i.e.*, before it has assumed the state of myosin.

Considered from this point of view the many mooted features of the process appear—it seems to us—under their proper light. Glycogen is absolutely known, first, to diminish during muscular contraction; second, to accumulate during rest; third, to rapidly decrease when an unfed animal is made to work. Notwithstanding these established facts, it is deemed inadequate, as judged from the analysis of *dead* muscle, to quantitatively satisfy the needs of the process. With oxygen as the initial factor it becomes clear that dead muscle only shows the residue of the combustion that has gone on during the progress of *rigor mortis*, and that the glycogen ratio should therefore include that of the sarcolactic acid,—to say nothing of other products of combustion that may be present,—which would bring the proportion of glycogen to a much higher figure than analyses under present conditions furnish.

Can we say, however, that glycogen alone satisfies the needs of the process? The fact that the most powerful of our domestic animals—oxen, horses, camels, elephants, etc.—are all herbivorous would suggest that such is the case. Again, it is the one constituent that is positively known to diminish during work and to accumulate during rest. All other sources, even fats, which are probably entitled to a place among the sources of muscular energy, have only been theoretically associated with muscular work, while the fact that the amount

of urea is not materially increased during muscular exertion tends to eliminate the proteids. Muscles from which glycogen is absent are stated to respond to stimulus; but the inherent irritability of muscle-tissue readily accounts for this. On the whole, experimental evidence, if considered in the light of the views herein advanced, tends to show that *glycogen is the main constituent of myosinogen with which the oxygen of the blood-plasma combines.*

The absence of free oxygen in muscle has been adduced as evidence to show that the carbonic acid evolved could not be formed by direct combustion. It becomes clear that if the oxygen is used up to the last—to such a degree that a muscle will absorb oxygen from the surrounding atmosphere—none will be obtained from its tissues, even with the air-pump. The transition of a muscle from its normal neutral reaction to an intensely acid one when the *rigor mortis* is fully established, is also accounted for by the oxidation of glycogen. Prolonged tetanus likewise causes acidity of the muscle; we have seen that this is due to excessive suprarenal activity: *i.e.*, to hyper-oxidation.

This subject is of such importance that we deem it advisable to meet each mooted point as presented by Professor Foster precisely as if the problems were placed before us for solution:—

1. "At the outset of *rigor mortis* there is a very large and sudden increase in the production of carbonic acid: in fact, an outburst, as it were, of that gas."

The onset of *rigor mortis* also represents the moment when vascular tonic contractions cease; the blood-vessels being suddenly dilated, a correspondingly great amount of oxidizing substance is as suddenly brought into contact with the energy-holding substances in the myosinogen, and an outburst of carbonic acid ensues.

2. "The increased production of carbonic acid during *rigor mortis* is not accompanied by a corresponding increase in the consumption of oxygen."

This conclusion, based on the consumption of oxygen in which the dead experimental animal is placed, does not take into account the oxygen stored in the animals' blood-plasma.

As shown in the first answer, the oxidizing substance in the latter is fully able to give rise to the production of the carbonic acid observed.

3. "A muscle (of a frog, for instance) contains in itself no free or loosely attached oxygen; when subjected to the action of a mercurial air-pump it gives off no oxygen to a vacuum, offering, in this respect, a marked contrast to blood."

A detached muscle is, as far as its vascular elements are concerned, similar to a muscle in which *rigor mortis* has begun. Its oxygen is not in sufficiently loose combination to yield to the dissociating action of the pump when stored in myosinogen, owing to its affinity for various constituents of the latter. While in *extra corpore* blood the oxidizing principle of the plasma might yield its oxygen *in vacuo*, it is probable that it will not, judging from recorded data, though it will do so to salicylic aldehyde, benzol, and benzilic alcohol, as shown by Schmiedeberg, Jaquet, Salkowsky, Abelous and Biarnés.

4. "When placed in an atmosphere free from oxygen it will not only continue to give off carbonic acid while it remains alive, but will also exhibit at the onset of *rigor mortis* the same increased production of carbonic acid that is shown by a muscle placed in an atmosphere containing oxygen. It is obvious in such a case that carbonic acid does not arise from the direct oxidation of the muscle-substance, for there is no oxygen present *at the time* to carry on oxidation."

The oxidizing substance when brought into contact with the myosinogen gives rise to an intramuscular reaction: one which, therefore, may continue in any atmosphere whether the latter contain oxygen or not.

Professor Foster then summarizes prevailing views as to this subdivision of the general subject, as follows: "We are driven to suppose that during *rigor mortis*, some complex body containing in itself ready-formed carbonic acid, so to speak, is split up, and thus carbonic acid is set free, the process of oxidation by which that carbonic acid was formed out of the carbon-holding constituents of the muscle having taken place at some anterior date."

The process appears to us to be fully accounted for as follows: *The presence of the oxidizing principle which the supra-*

renal glands indirectly furnish to the blood-plasma accounts for the phenomena witnessed. The abrupt increase in the production of carbonic acid after death is due to the sudden relaxation of the normal tonic vascular contraction incident upon the lethal state and to the equally sudden onslaught of oxidizing principle upon the myosinogen thus induced. Myosinogen becomes myosin after the intrinsic combustion processes have ceased.

But can functional activity be maintained in an organ merely by an increase of the local blood-supply? That such is the case may be shown by means of one of Claude Bernard's experiments,—that in which he demonstrated the existence of vasodilator nerves. Having severed the chorda tympani,—a branch of the facial distributed to the submaxillary gland,—he found that, when the peripheral segment of the cut nerve —that leading to the gland—was electrically stimulated, its normal function became manifest. Mathias Duval described the phenomena that immediately ensue as follows: "While the salivary secretion is thus increased, the blood-vessels of the gland are seen to become greatly enlarged; previously invisible arterioles become red and turgescent. If the main trunk of the gland is exposed, it is seen to increase in size, while its contained blood, *blackish before the experiment, becomes as red as arterial blood* the moment the chorda tympani is stimulated; indeed, if the vein is cut, the blood may be seen to flow in rhythmic jets, as it does from an artery, while it merely drools out when the gland is in the state of rest: *i.e.*, when the chorda tympani is not excited."

The organ selected for the illustration, the submaxillary gland, is particularly advantageous for the purpose, because its vasodilator nerve, the chorda tympani, is isolated from the vasoconstrictor branch of the sympathetic, also distributed to the gland: a feature of importance. Again, it is evident that function occurs without the active participation of the nerve-impulse *per se*, such as that associated with a "motor" nerve. We have, in Professor Duval's presentation of the process, an exact description of the mechanism of active function. There is not only increase of blood, but increase of energizing blood: *i.e.*, blood that is not allowed to become venous *in situ*. The carbonic acid evolved must at once be removed; hence the

rapid flow; while the veins are for the time being, as long as active functions continue, transformed into arterial channels. Briefly, more arterial blood means more work. As we will see later on, this is the only process through which the potential of any organ—*i.e.*, its latent power to do work—is maintained and its functional activity awakened when required. Whether the structures involved be muscular, hepatic, gastric, renal, cerebral, splenic, etc., the exciting factor of activity is always—shall we say *blood?* No; all this evidence emphasizes the fact that *the oxidizing substance is the main factor of all functional processes,* and that *the red corpuscles are but carriers of oxygen intended to sustain the plasma's efficiency as an oxidizing body.* We have seen that Salkowski was also led, but by chemical methods, to deny the red corpuscles the all-important rôle now ascribed to them.

The Motor Nerves and their Rôle in Muscular Contraction.—We must now transfer our attention to the "vasoconstrictor" side of the question. The sciatic nerve is thought to be supplied with vasodilator and vasoconstrictor fibers. Division of this nerve causes the usual widening of the arteries, while electrical stimulation of the peripheral nerve-end causes contraction of the dilated arteries. This coincides with the experimental results of section of the cervical sympathetic, the splanchnic, etc., already given. "But sometimes a different result is obtained," says Foster, "on stimulating the divided sciatic nerve: the vessels of the foot are not restricted, but dilated—perhaps widely dilated": a phenomenon which leads him to conclude "that the sciatic nerve (and the same holds good for the brachial plexus) contains both vasoconstrictor and vasodilator fibers," and to interpret the varying results as due "to variations in the *relative* irritability of the two sets of fibers."[4] These remarks are only intended by their author to convey, not a personal conclusion, but an inferential deduction based on what testimony the experiment referred to affords as to the existence, in the sciatic and brachial plexuses, of both constrictor and dilator fibers. It is the value of the testimony itself, and not the author's deduction, therefore, that we are analyzing.

[4] The italics are our own.

A query that normally suggests itself is the following: What is the experimental value of the current for the determination of the specific function of *any* nerve when its *relative* irritability is a sufficiently prominent factor to cause it to indicate, under the influence of this current, one function at one time and the opposite function the next? Evidently the variation in irritability must mean either—as is the case with the nerves of the parotid gland—that the antagonistic nerves are directly connected or juxtaposed or that one is sufficiently metamorphosed organically as to modify its conductivity. Framed in this manner, the query meets with a ready response: Inasmuch as vasoconstrictor and vasodilator nerves *accompany* the sciatic nerve, they become *common* conductors when the circuit is closed, and any indication furnished, therefore, is of no scientific value.

There is another possible explanation, however, viz.: Either one of the dilator or constrictor nerves may be absent in the structures supplied by the sciatic and the brachial plexus. In other words, skeletal muscles may only be supplied with one of these nerves. Yet there is no experimental difference between these and other structures of distribution; thus, section causes vasodilation, while stimulation gives rise to constriction of the vessels, and, if either of the vasomotor nerves is not supplied to these structures, their motor nerves must fulfill the rôle of the absent system. We could readily enough state, after eliminating the only evidence in favor of the existence of vasoconstrictors, that there are none in striated muscles, all the positive evidence pointing only to the existence of vasodilators. But we must not lose sight of the fact that we have interpreted the experimental evidence at our disposal in a different manner, and that our own views must also be shown to be in accord with this evidence, if they are to merit confidence.

From our standpoint, then, granting the existence of both constrictor and dilator nerves, in direct relation with the sciatic, what would be the result of electrical stimulation? *None, whatever*,—diameter, structure, and peripheral elements of the nerves being equal. Function depending on increased blood-supply and perfect balance between vasodilation and con-

striction being the fundamental requirement of normal activity, the conductivity of both nerves must be equal; hence, this position may be taken as a working basis. But quite another result is to be expected when, as is actually the case, the sciatic is to be considered as a factor of the problem. A large motor nerve *plus* the constrictor *plus* the dilator no longer represents balance as to conductivity, and our analysis must now include, as an element, the fact that the energy distributed to the vasodilator nerve will, all else being equal, be as its circumference is to that of the sciatic and the vasoconstrictor combined. When the great size of the sciatic is recalled, it becomes evident that the dilator will at best receive an insignificant proportion of the current. Under these circumstances what experimental results could we expect? Section would obviously cause dilation, since the dilator nerves would be cut, and the tonic contraction of the vessels would also be annulled through section of the constrictor. Electrical stimulation of the peripheral stump of all the nerves, therefore, could have but one result,—constriction,—since the dilators receive practically no current. This agrees perfectly with observed facts. But why the opposite result also observed? This renders it necessary to analyze what evidence there is as to the actual existence of vasoconstrictors in striated muscles.

"With regard to the vasoconstrictor fibers," says Professor Foster, "*the only evidence* that they exist in muscles is that when the nerve of a muscle is divided the blood-vessels of the muscle widen, somewhat like blood-vessels of the ear after division of the cervical sympathetic. This suggests the presence of vasoconstrictor fibers carrying the kind of influence which we called tonic, leading to an habitual moderate constriction; it cannot, however, be regarded by itself as conclusive evidence." We have seen that vascular constriction is unmistakably associated with the sympathetic system: its only source elsewhere. No fibers of the sympathetic are associated with skeletal muscular tissue. In fact, Professor Foster, referring to the latter, says: "The presence of any vasoconstrictor fibers at all has not at present been satisfactorily established. When a muscle contracts there is always an increased flow of blood through the muscle," thus simultaneously suggesting the pos-

sible absence of vasoconstrictors and indirectly confirming the presence of vasodilators.

The question, therefore, becomes an open one, and, if it is considered from the standpoint of our conception of the process of muscular contraction,—*i.e.*, with the vasodilators as the inciting factor of the oxidation process that underlies muscular activity,—the contradictory phenomenon referred to—*i.e.*, *dilation* under electrical stimulation—may be accounted for, provided, however, vasoconstrictor nerves are eliminated from the function involved.

Foster states that "this vasodilator action is almost sure to be manifested when the nerve is divided and the peripheral stump stimulated *some days* after division, by which time commencing degeneration has begun to interfere with the irritability of the nerve. For example, if the sciatic be divided, and some days afterward, by which time the flushing and increased temperature of the foot following upon the section has wholly or largely passed away, the peripheral stump be stimulated with an interrupted current, a renewed flushing and rise of temperature is the result." As *we* interpret this result, the stimulation means vasodilation. But we have stated that the sciatic, owing to its greater size, would practically alone transmit the energy, leaving the vasodilator uninfluenced, and, if we transfer to the sciatic the constrictor function, the effect should be the opposite of that observed. That a better conductor than the vasodilator is present is shown by the sentence "the constrictor fibers also appear to be more readily affected by a tetanizing current than the dilator fibers." The sciatic itself being looked upon by us as the vasoconstrictor, we can, therefore, connect the remark with this nerve. Bearing this fact in mind, we will now inquire into the comparative behavior of the sciatic as a motor-constrictor nerve with its antagonist, the vasodilator, under the conditions mentioned: *i.e.*, section, followed some days later by stimulation, utilizing quotations from Professor Foster's text as the basis of our analysis.

Referring to the sciatic and brachial plexus, he says: "The constrictor fibers appear to predominate in these nerves, and hence constriction is the more common result of stimulation."

Considered as motor constrictors these nerves would respond to stimulation in precisely this manner. "Exposure to a low temperature again seems to depress the constrictors more than the dilators; hence, when the leg is placed in ice-cold water stimulation of the sciatic even when the nerve has been but recently divided, throws the dilator only into action, and produces flushing of the skin with blood." This demonstrates at least an intimate association between motor and constrictor functions. Again, since placing of the limb in ice-cold water abolishes response of the sciatic to stimulation, this nerve must readily succumb functionally to untoward influences—evidently sooner than the vasodilator. This is confirmed by the statement: "The latter" (the vasodilators), "in *contrast* to ordinary motor nerves, retain their irritability after section of the nerve for very many days." Again does the link between the motor and the constrictor element appear, and as they jointly succumb while the dilators retain their irritability, and the loss of function under pathogenic influences begins much sooner than in the latter, we are brought to recognize, first, that motor and constrictor nerve-elements are either pathologically affected in precisely the same manner, or that both functions are attributes of the motor nerve; second, that we have in the histological changes incident upon section of the latter, or the nerves of the brachial plexus, the cause of vascular dilation that ensues upon stimulation, when this experimental procedure is not carried out at once.

And, indeed, the strength of this proposition appears if we examine the histological structure of any nerve-bundle, and particularly such organs as the sciatic. The many elements that enter into their organization suggest immediate morbid alterations on section, especially if our view that the blood-plasma is the vehicle or excipient of the oxidizing substance which maintains all functional processes is warranted. Under these conditions, it is plain that cutting of the nerve should at once initiate degenerations, the morbid process and the resulting loss of functional powers progressing until, "at a certain stage, a stimulus, such as the interrupted current, while it fails to affect the constrictor fibers, readily throws into action the dilator fibers."

But why do the dilator fibers not degenerate likewise? Inasmuch as, quoting Professor Foster's words, "the presence of any vasoconstrictor fibers at all has not at present been satisfactorily established," while "the only evidence of their existence" is that, "when the nerve of a muscle is divided, the blood-vessels of the muscle widen," we must admit, in the face of the foregoing statements, that all the evidence now tends the other way: *i.e.*, to suggest that the sciatic and the brachial-plexus nerves are not only motor, but "motor-constrictor" nerves, and that dilators are autonomous structures—if they exist at all.

Referring to the effects of severance of a nerve from the central nervous system, Foster says: "When a nerve—such, for instance, as the sciatic—is divided *in situ*, in the living body, there is, first of all, observed a slight increase of irritability, noticeable especially near the cut end; but after awhile the irritability diminishes and gradually disappears. Both the slight initial increase and the subsequent decrease begin at the cut end and advance centrifugally toward the peripheral terminations. This centrifugal feature of the loss of irritability is often spoken of as the Ritter-Valli law. In the mammal it may be two or three *days;* in a frog, as many, or even more *weeks*, before irritability has disappeared from the nerve-trunk. It is maintained in the *small* (and especially in the intramuscular) branches for still longer periods." This obviously suggests that *the size* of a nerve, all else being equal, is a governing factor in the degenerative process due to nerve-section, precisely as indicated when the relative effects of the electric current were referred to.

Still, such a governing principle would necessitate that a large nerve be structurally similar to a small one, qualitatively and quantitatively, to warrant our accepting it as the basis of a final conclusion. Such is not the case, however, as is well known. While the various structures that enter into their formation are specific to nervous organs, they are not evenly distributed. This is illustrated in the case of vasomotor nerves. Though both constrictors and dilators are medullated, the former lose their medulla *early* in their course, while the vasodilators preserve theirs until the blood-vessels to which they

are distributed are *almost reached.* We must also remember that this medulla is an extremely complex body. "Being so complex," says Professor Foster, "it is naturally very unstable, and, indeed, in its stability resembles putrid matter. Hence, probably, the reason why the medulla changes so rapidly and so profoundly after the death of the nerve." Viewed from our standpoint, this suggests that, inasmuch as the vasodilator fibers preserve their medulla until the vessels to which they are distributed are nearly reached, they should degenerate *before* the constrictors, which lose theirs early in their course. And such would be the case *did any such nerves exist* in the sciatic or brachial-plexus nerves or any nerve of the skeletal muscular system. Indeed, were there any, their functional activity would outlive that of the vasodilators, which is not the case. If this fact is now considered in association with the other features of this analysis, it seems to us to suggest that *the voluntary muscular system is not supplied with separate vasoconstrictor nerves,* and that *the functions of the motor nerves distributed to these muscles include that of vasoconstriction.*

Further evidence that this conclusion must represent the actual state of things is afforded by the manner in which it simplifies—provided, of course, previous conclusions are likewise admissible—the whole process which underlies voluntary muscular activity, without in any way contradicting the data sustained by experimental evidence. Indeed, vasoconstrictors have never been found; an element of confusion is thus removed which will probably enable us to ascertain the actual effects of nerve-impulse on the voluntary muscular fibers and their purpose. As to the vasodilators, another element of confusion is removed through the fact that we now know from data recorded in these pages that they need extend no farther than the ultimate vascular subdivision, the walls of which contain muscular elements: *i.e.*, the arterioles. The fact that the oxidizing substance of the blood-plasma reaches the muscular elements themselves and can there exercise its life-sustaining power and suddenly awaken activity also simplifies a very perplexing question. The capillaries which entwine the muscle-fibers simply allow their plasma to ooze out through their stomata, or endothelial-plate interstices, and to thus reach the

contractile substance through the latter's own investing membrane. Increase of plasma means increase of work: *i.e.*, muscular contraction. Waste-materials are as rapidly returned through efferent capillaries to the venules, thus leaving the field clear for continuous function.

While we have perhaps simplified the processes mentioned, we have complicated another, since we now find it necessary to account for the functions implied by "voluntary," "motor," and "constrictor," all through the operation of one set of nerves. And yet we are now in perfect accord with the anatomical side of the question, since there is no evidence that constrictor nerves exist. The *only* nerve distributed to a voluntary or striped muscle proper, the motor nerve, enters its sheath, breaks into numerous subdivisions, and thus sends one filament—occasionally two—to each muscular fiber. On the surface of the latter, near the middle, an important terminal arrangement prevails: *i.e.*, each nerve-fiber develops its "motor end-plate." Its white matter of Schwann ceases and its outer covering becomes continuous with that of the muscle, so that its axis-cylinder alone penetrates to the muscular fiber. Here it subdivides into numerous root-like processes, forming a hillock, or motor end-plate, supported by a layer of granular substance which contains a number of large nuclei. It is this end-plate that the impulse first strikes when it reaches the muscular fiber, and it travels from the center of the latter to the two ends. All the elements of the muscle are so disposed as to receive the impulse simultaneously.

Before analyzing the mechanical result of this impulse or going further into the vasodilator question, a brief allusion to the histology of the arterioles of voluntary muscle must be made. The internal coat is composed, as elsewhere, of endothelial cells; when the middle coat is cut transversely, however, it presents a peculiar conformation: *its outline festooned.* Ranvier[5] divides the middle coat into two layers: an internal elastic lamina and a muscular layer. In his description of these structures he says: "The internal elastic lamina, as is the case with all parts formed of elastic substance, possesses

[5] Ranvier: quoted by H. Berdal, "Histologie Normale," 1894.

but little elasticity, and, when it is compressed by the muscular layer encircling it, it happens that the lowest limit of its elasticity is surpassed and that, in order to accommodate itself to the restricted space reserved for it, it forms folds. It is for this reason that a transverse section causes it to appear as if festooned, while longitudinal sections of these small arteries, owing to folds formed during muscular retraction, give the appearance of longitudinal striæ." From our point of view this is subject to another interpretation. Indeed, this festooning in *longitudinal* folds,—observed to a limited extent in all small arteries,—coupled with the effects of muscular retraction, seems to us to distinctly point to the mechanical process through which efficient changes in the caliber of the arterioles are insured.

The impulse, we have seen, travels from the end-plate toward the extremities of the muscular fiber and the muscle contracts, according to our view, as the result of dilation of the arterioles. While the sudden onset of oxidizing plasma, by suddenly increasing the production of chemical energy, which in turn is converted into contractile energy, accounts for the latter, it does not account for the "voluntary" element of the process, nor for the wonderful precision which characterizes muscular movements—those of the fingers, for instance. Indeed, myosinogen *plus* the oxidizing substance must be considered—if our doctrine prevails—as the only source of work, but not as the intermediary through which the volition (conscious or unconscious) implied by the word "voluntary," and the functional control that this implicates, is obeyed. In other words, it constitutes what in the locomotive is represented by the combination of fire, water, and steam, but it does *not* represent the throttle-valve, which is subject to the will of the engineer. His "voluntary" act, transmitted through the lever, regulates the quantity of steam admitted into the cylinder—in which heat is transformed into work. In the muscle each "fine, transparent, membranous tube" is a cylinder, but one in which the conversion of energy into work is the result of a local process in which myosinogen *plus* the oxidizing substance are the *sources* of energy. The throttle-*valve* is obviously the arteriole, but so located as to admit—as

regards contraction—a surplus, not of fuel, but of the active element which underlies the effects of "draught" in the engine: *i.e.*, oxygen, that contained in the "oxidizing" substance. The fuel—myosinogen—is always present in our muscles—when they are normal, and the activity of the combustion is regulated there, as elsewhere in Nature, by the quantity of oxygen admitted. Yet, how is the conscious or unconscious control implied by the word "voluntary" carried out?

The muscular arteriole during complete muscular retraction is only just sufficiently patent to allow the passage of enough blood-plasma containing the oxidizing substance to sustain the nutrition of the muscular tissues, and other processes through which their functional efficiency is insured. But the fact must not be overlooked, as emphasized by Foster, that the relaxation is an essential part of the whole act; indeed, no less important than the shortening itself. Again, a completely retracted muscle is not a relaxed muscle; it is precisely in the opposite state,—*i.e.*, in a condition of tension between its insertions,—and if either one of the latter be cut the muscle recedes toward the other. This feature is well exemplified after amputations. The biceps can contract unimpeded, for example, three times the extent that its skeletal attachments will normally allow; fractures of the olecranon or of the patella are familiar examples, notwithstanding the fact that the muscles thus liberated at one end are held partly retracted by the surrounding structures. Indeed, a normal muscle can aptly be compared to a piece of rubber stretched between two fixed points, and contraction really represents a relaxation of the stress. But there are variations in the resistance to which this stress is submitted, and it is here that the identity of the controlling concept appears as an independent factor, while that of the motor mechanism also emphasizes itself by phenomena that cannot logically be considered as elements of the process through which the "voluntary" impulse is transmitted, nor of the transmitting organs, the motor nerves.

If the arm is flexed, say, at an angle of 90 degrees, it can be held in this position without fatigue for some time. But if a sufficiently heavy weight be placed in the hand, the arm remaining in precisely the same position, marked evidences of

strain appear: the face becomes flushed, the superficial veins enlarge, more or less sweating occurs, etc.: *i.e.*, all the familiar signs associated with continued effort assert themselves. Resistance evidently underlies the whole process, and, as "resistance" always implicates at least two contending forces, we are led to divide the process itself into two parts: *i.e.*, the weight which tends to force the hand down and the muscular effort exerted to hold it up. But if we analyze the muscular effort, it soon becomes apparent that it is itself susceptible to a clearly defined subdivision. Indeed, notwithstanding the weight, the arm *remains fixed* in one position; and the entire organism shows the effects of strain; muscles other than those of the arm contribute work, the entire circulatory system (including the heart, judging from its overaction) enter into a phase of unusual activity, etc.,—all laboring to the one end, viz.: to mechanically satisfy, regardless of the aggregate of energy converted into work, the needs of the voluntary act *physically impressed upon the muscle* and transmitted to it from the brain through the motor nerve. We thus have, on the one side, a form of volitional energy through which the muscle is *fixed* in the one position; and, on the other, an oxidation process, through which muscular work is carried out, sustained, and intensified to the highest possible degree compatible with the body's strength.

That two distinct processes are present may be shown in several ways. Professor Foster, referring to the "*impulse-wave*," states, for example: "It is *followed* by an explosive decomposition of material, leading to a discharge of carbonic acid, etc." Not only does the active reaction occur *after* the dispersion of the impulse, but Helmholtz ascertained that quite a perceptible and computable period of time elapsed between the two phenomena. By means of the Marey myograph this "latent period" was found to occupy one-sixtieth of a second, while the maximum contraction is only reached at the end of about one-sixth of a second[6] in an average muscle. A radical difference is also evident in the relative ability of the two kinds of energy—volitional and motor—to undergo fluct-

[6] M. Duval: *Loc. cit.*, p. 151.

uations in what, for the sake of convenience, we may call "intensity." The impulse-wave simply *sets* the muscle-elements to a given vibratory rhythm, and they retain this, whatever be the intensity of the exertion required. The oxidation process, on the contrary, contributes whatever degree of mechanical energy is necessary to fulfill the needs, not only of the movement, but also of any additional work an increase of resistance may demand. Thus, the impulse-wave may fix the muscles of the flexed arm in a given position, but any fluctuation in the power required to support different weights is at the expense of the motor mechanism. This may be aptly compared to the manner in which a note on a violin is made loud or soft. The power with which the string is pressed upon with the moving bow modifies the intensity of the sound; but the note remains the same. This means that its *pitch* does not vary, and if, for example, the lower C is given, we will know that the *sound-wave* of that note represents 261 vibrations per second. So may the *impulse-wave* transmitted by the brain through a "motor" nerve be represented by a fixed number of vibrations. Retraction, the muscle being then most tense, is therefore characterized by the greatest number of vibrations. On receiving the impulse the muscle adjusts itself, whether by contraction or retraction, to precisely the extent which the number of vibrations transmitted will allow, and remains *fixed* in the state of contractility assumed until the impulse-wave itself is modified. The *power* or *intensity* of sound and the variations in the work this implies are fully typified by the motor process, through the enhanced circulatory activity and a corresponding increase in the *rapidity* with which the oxidizing substance is brought into contact with the myosinogen in the muscles. It is simply a question here of more fuel and more draught.

Obviously, the rhythm transmitted to a voluntary muscle is simultaneously communicated to the muscular walls of its vessels by the same impulse. The lumen of each vessel—veins as well as arteries, since the former also possess a muscular coat, but much less important structurally and therefore less active—varying synchronously with the muscle to which it is distributed. the flow of blood through it is exactly adjusted

to the needs of any degree of muscular contractility the voluntary (conscious or unconscious) movement requires. In other words, *the arteries, and to a certain extent the veins, become constricted or dilated proportionately as the muscle is contracted or retracted,* and the activity of the motor mechanism is thus concurrently adjusted to the functional requirements of the moment.

If this conception is not erroneous, the general process it represents certainly constitutes a marvelously simple way of accomplishing many of the most important functions of the organism, since those ascribed to both vasoconstrictor and vasodilator nerves are thus performed without, indeed, leaving a single reason for the presence of *either of these nerves* as independent entities.

This normally suggests the question: Do vasodilators actually exist in muscular vessels? That there are vasodilators in certain organs: the submaxillary and other salivary glands, the tongue, the penis, etc., is thought to have been experimentally demonstrated; but their existence in the muscular vessels has not been shown, the evidence adduced, as was the case with the constrictors, being purely inferential. We have seen that section of the sciatic, followed by stimulation after some time had elapsed, caused dilation of the vessels of the extremities, while earlier it had caused constriction. Close analysis also showed that actual dilation of the arteries could be ascribed only to an *active* dilator action. The only remaining feature that requires elucidation, therefore, is the manner in which this is carried out. Does the above-described process account for these contradictory phenomena as well as would vasodilator nerves? That the elastic lamina of the vessel can fulfill precisely the same function as the latter seems evident.

The impulse-wave being accepted as the governing factor, each point of the muscular coat is caused to recede or approach from the axial line of the vessel just sufficiently to bring the caliber of that vessel to the required limits. Hence the presence of the muscular coat *over* the elastic lamina. The cause and purposes of the latter's longitudinal corrugations now become apparent: while perfectly elastic, it is somewhat larger in diameter than the muscular layer, and, lying, as it does,

within the latter, it forms the folds or "festooning" described by Ranvier. Viewed from our standpoint, however, these longitudinal folds play a very important part in the whole mechanical process described, since it is upon variations of their outline that the adjustment of the lumen of the vessel mainly depends. Mere dilation of a circular vessel, of course, involves an increase in the diameter of the stream passing through it; but, if numerous folds that project into that stream are simultaneously withdrawn by being leveled out, it is evident that the free space within the vessel will be vastly increased, and that a much greater range between dilation and contraction will thus be available.

That such is the process through which a slight variation of the peripheral pressure exerted by the muscular layer will cause a relatively larger variation of the amount of blood to pass through the vessel seems very probable, since it satisfies all mechanical needs. As long as the characteristic impulse-wave of a fixed degree of muscular contraction persists, the vessels are simultaneously adjusted to the needs of this particular degree of contraction and allow just the necessary amount of blood—*i.e.*, oxidizing plasma—to pass.

Returning now to the contradictory results of stimulation of the sciatic after section of that nerve, an important feature must be referred to, which, if considered before, would have but introduced confusion in the inquiry: *i.e.*, the fact that stimulation of this nerve immediately after section may either be followed by dilation or constriction. Laryngologists are quite familiar with the fact that one strength of current will cause adduction of the vocal bands,—*i.e.*, of their muscles,—while another strength will cause the opposite condition—abduction,—when the recurrent laryngeal nerve is cut and stimulated. That the same controlling factor must prevail in the case of the sciatic is very probable, if, as we have suggested, the rhythm of the impulse-wave determines the degree of muscular contraction. The certainty with which dilation is produced when the nerve is stimulated "some days after division" is a phenomenon of another sort. The electric current does not, like a normal nerve-impulse, select a physiological path; it simply utilizes the channels that offer the least resistance.

A diseased sciatic means impairment not only of its conductivity, but also of that of its subdivisions. The current may or may not, under these conditions, continue to follow the nerve stimulated after the segment buried in the tissues is reached; selecting the best conductors, it will, if it follow the course of the vessels, mainly stimulate the layer offering the least resistance: *i.e.*, the thickest and softest, as regards inherent proportion of fluids. As this characterizes the elastic layer, it cannot but receive the brunt of the stimulus. We are no longer dealing with muscular vibrations, but with a corrugated elastic tube the normal tendency of which is to expand, level its folds, and *increase* its lumen. The current, by inducing erethism, encourages this, and produces, by increasing the caliber of the vessels, "flushing and increased temperature of the foot." Indeed, electricity is a poor substitute for the physiological impulse-wave and sometimes a misleading one.

We can fully agree with Professor Foster, therefore, when he says: "There is no adequate evidence that these vasodilator fibers serve as channels for tonic dilating impulses or influences," and express our personal opinion that *neither vasoconstrictor nor vasodilator nerves exist as separate entities in voluntary muscles, both functions being fulfilled through the agency of their motor nerves.*

The following general deductions seem to be warranted by the facts presented:—

The functional activity of a voluntary muscle is dependent upon the following correlated factors:—

1. As to nervous stimulus: *an impulse-wave transmitted from a cerebral center through motor nerves, which adjusts the muscle to a fixed degree of contraction. As the vibratory rhythm of the impulse and that of the muscle always correspond, any variation of rhythm by the brain-center correspondingly modifies the muscular contraction.*

There are no independent vasoconstrictor or vasodilator nerves in voluntary muscles, both functions being fulfilled by the motor nerves through the filaments distributed to the muscular coat of the vessels of these muscles, and under the influence of the same impulse-wave that adjusts and fixes the latter's contraction or retraction.

Source of muscular energy: *an oxidation process in the muscular contractile elements the chemical energy of which, after conversion into mechanical energy, supplies the muscle during any stage of contraction or retraction with the power-to-do-work required to sustain either of the latter.*

This oxidation process is subject to fluctuations of activity, and occurs as the result of a reaction between two physiological compounds: first, myosinogen,—i.e., blood-plasma containing various carbohydrates and immanent in the muscle-fiber,—as a potential; second, an oxidizing substance, also contained in the blood-plasma, but in that of the arteries, as reagent.

2. As to mechanical process: *variations in the caliber of the muscular vessels give rise to corresponding variations in the proportion of oxidizing substance admitted to the myosinogen in the muscular fiber and to correspondingly marked fluctuations in the activity of the oxidation process.*

The myosinogen is stored in the contractile disks while the oxidizing plasma fills the interstitial disks, and an opening between the two probably exists through which the oxidizing plasma is forced when the impulse-wave adjusts the muscle to the required contraction, the quantity of energy produced being thus simultaneously adjusted to the needs of that contraction.

THE OXIDIZING SUBSTANCE AND THE MOTOR NERVES IN THEIR RELATION TO GLANDULAR SECRETION.

In the foregoing pages we have sought to elucidate the manner in which the voluntary muscular system could be endowed with vasomotor functions. The result has suggested that such a system as the sympathetic does not exist as a separate entity, and that the double chain of ganglia on each side of the spinal column, and those situated in the head, thorax, abdomen, and pelvis, their intercommunicating nerves and plexuses are, in reality, but subdivisions of the motor system. We have ascertained that a motor nerve was a vasodilator or constrictor only in the sense that it adjusted the organ's functions to a specific degree of activity, and simultaneously adjusted the lumen of its vessels to the needs of this functional activity in order to admit precisely the amount of blood—*i.e.*, of oxidizing serum—required. Obviously, each

organ contains, as inherent source of energy, either endogenous products with which the oxidizing substance combines, or cellular structures whose metabolism is sustained by the oxidizing substance. This is a question, however, that will be taken up as each organ is studied.

The classic subdivision into two great systems, cerebro-spinal and sympathetic, seems to us, therefore, to be subject to modification. Indeed this subdivision has always been an artificial one, since at all times some connection or other with the cerebro-spinal axis, whether it be associated with borrowed or direct impulses, has always had to be considered as a factor of its functions. This is well illustrated in a comprehensive paper, in which the functions of the sympathetic system are ably reviewed, by B. Onuf (Onufrowicz) and James Collins,[7] who refer to tonic vascular contraction as follows: "It has been shown that many nerves of the sympathetic system are under the tonic influence of spinal or cerebral centers. Section of the cervical sympathetic nerve is followed by dilation of the blood-vessels of the head; section of the abdominal sympathetic by dilation of the blood-vessels of the hind-paws; section of both splanchnics by the same phenomena in the stomach and the intestine. Severance of the nerves connecting the submaxillary ganglion with its encephalic center gave rise to an increasing continuous secretion of the submaxillary glands, proving the regulatory influence of the cerebro-spinal system upon the submaxillary ganglion (Claude Bernard)."

If we now recall the limitations of the adrenal system described in the last chapter,—*i.e.*, the triad: thyroid, anterior pituitary, and adrenals,—and particularly the connection between the two latter organs through the chain of sympathetic ganglia and the splanchnic nerves, the following remarks of the same authors are especially interesting: "Regarding the tonic influence of ganglia of the sympathetic itself, the views still differ. . . . We know, however, that the heart removed from the body still continues to beat, and that the bladder deprived of motor nerves leading to it continues to perform its functions." They also refer to the observations

[7] B. Onuf and James Collins: Archives of Neurology and Psychology, vol. iii, Nos. 1 and 2, 1900.

of Contejean, "according to which the secretion of gastric juice continues after the stomach has been deprived of all its nerve-connections." The reason for this is now clear. Inasmuch as the motor nerves merely *excite* to action and *regulate* this action through their impulses, severance of the nerve-supply of an organ only annihilates this function, and, as the agency that supplies it with working energy reaches its tissues through the blood, it is plain that its functional activity should continue, even when its motor nerves are severed.

As regards the tonic contraction of vessels ascribed to the sympathetic vascular fibers, it is merely the result of the *continuous*, though passive, activity in which all muscular tissues are held by the oxidation process, which continues as long as blood flows in physiological channels. This includes the increasing, though perhaps slower, filtration of oxidizing plasma into the contractile elements of the muscular fibers of the vascular walls, and its return to the blood-stream *per se* charged with products of combustion. As previously stated, these do not only represent the products of hydrocarbon combustion, the specific source of muscular energy, but also those resulting from metabolism of the cellular elements *per se*. In other words, a relatively small amount of oxidizing plasma is incessantly penetrating to the myosinogen and causing the development of just sufficient energy to insure nutrition of the tissues and to keep them in that *potential* state in which, though not doing active work, they are ever ready to actively respond to summonses: *i.e.*, to "motor-nerve" impulses. A skeletal muscle, held by its two insertions, is not free to contract in obedience to what energy the continuous oxidation process generates, and, not being at once converted into work, this energy is dissipated as heat. But not so with the vascular walls; having only the centrifugal resiliency of their inner coat to contend with, they at once convert the chemical energy generated by the reaction in their contractile elements into work which manifests itself as "tonic" contraction.

We have stated that voluntary muscles possessed no vasoconstrictor or vasodilator nerves *per se*, and that the functions ascribed to such nerves were exercised through the agency of the "motor" nerves. What is now termed a vasoconstrictor

nerve, therefore, is, according to our view, nothing but a motor nerve distributed to the muscular coat of the vessel. Does this also apply to the vascular supply of the internal organs? We have ascertained that the existence of the vasomotor nerves in the parts studied was purely inferential. If works on anatomy are consulted—*i.e.*, works in which actually-present structures are described—no reference to a special set of nerves endowed with vasomotor functions is made. The subdivisions of the sympathetic are deemed to be the vasoconstrictors; as to the vasodilators, apart from those distributed to the submaxillary and parotid glands, the tongue and the auricles, all still belong to the domain of conjecture.

If our view is based on a solid foundation, we must, however, be able to show that all the nervous structures comprised under the name of "sympathetic" are component parts of the general *motor* system and that they are not only capable of causing constriction, as now generally believed, but also dilation of the structures to which they are distributed. We have seen, for example, that when the cervical sympathetic chain is severed, the phenomena are those already referred to dilation of the vessels of the ear, which can be overcome by stimulation of the cephalic end of the cut nerve. We must also account for the phenomena witnessed at least as well as they are by the older doctrine. In this experiment it is plain that the dilation of the vessels ensues owing to the *loss* of their regulating nerve-impulse. The fact that the local temperature rises shows that the oxidation process is independent of the impulse, since it continues nevertheless. On the electric current being applied the nerve-impulse is replaced, the recontracted vessel overcomes the exaggerated blood-flow, and normal conditions are restored. Of course, we shall have to introduce various phenomena, now attributed to the sympathetic nerves, which belong to the domain of the suprarenal glands and perhaps to the other organs of the system described in the last chapter, since it is only by clearly defining the part taken by each set of organs involved that we can, if not elucidate the subject itself, at least make our position clear.

We are fortunate in having at our disposal in this connection the article, previously referred to, by B. Onuf (Onu-

frowicz) and Joseph Collins,[8] in which experimental researches on the central localization of the sympathetic system are related. It contains, besides a critical review of the anatomy and physiology of this system, several references to the morbid conditions to which we have alluded.

After a very brief reference to the many observers who have given the sympathetic system especial attention, including Pourfour du Petit, Claude Bernard, Schiff, Vulpian, Dastre and Morat, Luchsinger, Heidenhain, Gaskell, and Langley, they outline its functions as follows: "It may safely be concluded that it has, to a great extent, a controlling influence over the secretion of most of the glands, the lacrymal, the salivary, the sweat- glands, the glands of the stomach and intestines, the liver, the kidney, etc.; that it presides over the circulation by regulating the caliber of the blood-vessels and the action of the heart; that it influences respiration; and finally that all the involuntary muscles, those of the digestive apparatus, of the genito-urinary system, of the hair-follicles (pilomotor nerves) are under its control."

We shall successively review each of the functions referred to, beginning with those that present the simplest mechanism,—*i.e.*, the lacrymal, salivary, sudoriferous, and mammary glands,—and seek to conciliate what new features our work has so far suggested with what experimental data we may be able to find. Whatever physiological teachings will appear weak,—*i.e.*, acknowledged to be so by physiologists,—we shall ascertain whether our views do not furnish some clue that may prove more satisfactory to them.

Lacrymal Glands. — Present knowledge as to the innervation of glands in general, judging from a perusal of its literature, is well exemplified by Matthews, who, after a careful study of the question, says: "Whether secretory nerves exist or whether secretion is ever a function of the gland-cell must be considered at present an open question."

To elucidate the connection between the sympathetic and the lacrymal gland Onuf and Collins removed one stellate[9]

[8] B. Onuf and Joseph Collins: Archives of Neurology and Psychopathology, Nos. 1 and 2, vol. iii, 1900.

[9] In the cat this ganglion constitutes what in man would be the three cervical and the first thoracic ganglia coalesced.

ganglion from each of three cats, and reviewed their results as follows: "In one of the cats (three and a half months old) an injection of 1 centigramme of pilocarpine, given three weeks after the operation, produced lacrymal secretion of the eye of the normal side, while the eye of the operated side remained dry. In the second cat (about two months old) 5 milligrammes of pilocarpine were injected one month after the removal of the left stellate ganglion. In this case the result was altogether different. Both eyes wept, but the eye of the operated side more profusely than the other. About an hour after the injection there was still considerable lacrymal secretion from the eye of the operated side, while the other eye was dry. In the third cat (about six weeks old) an instillation of a 2-percent. solution of pilocarpine was made in both eyes, four and one-half months after the operation. The effect was an equal amount of lacrymal secretion in both eyes." The authors then close the subject with the following remarks: "These results are rather contradictory, and further experimentation must be made to harmonize them and to allow of a correct interpretation. It must be taken into consideration, of course, that the age of the animals varied, as did also the period (after the operation) at which the pilocarpine was administered. The manner of administration of the poison was different also."

Viewed from our standpoint, these experiments do not appear contradictory; indeed, they may enable us to ascertain the identity of the nervous structures involved and the manner in which the functions of the gland are carried out. Obviously, removal of the stellate ganglion on the one side severed the connection between the anterior pituitary lobe and the adrenal on that side. Pilocarpine injections, by stimulating the anterior pituitary, caused the latter to transmit activating impulses through the perfect ganglionic chain to the terminal adrenal of that chain; but, the secretion of both adrenals being poured into the one channel, the end-result of the injection of pilocarpine, as regards its effects upon the lacrymal glands *per se*, was merely a reduction of the intensity of the local symptoms, through a corresponding reduction of the vascular-pressure increase which both glands would have produced. Still, judging from its effects upon the normal lacrymal gland,

the pilocarpine must certainly have stimulated the functional activity of the organs through the blood. That the adrenals, or at least the normal adrenal, were involved in the process is suggested by the actual phenomena witnessed in the animals and the gradual increase of power assumed by the adrenal on the normal side, as time elapsed. In the first cat, for instance, the injection was given three weeks after the operation, and the eye on the operated side remained dry. In the second, a younger one, one-half the dose given the first cat was administered one month after the operation; this violently stimulated the normal adrenal and so increased vascular pressure that lacrymation occurred on both sides—especially on the operated side, since the vessels had lost their tonicity. The muscular coats of these vessels in the first cat had not been contracted, the dose given it having caused insufficiency of the adrenals; but the smaller dose administered to the second animal having given rise to stimulation of these organs, lacrymation occurred. In the third cat, the injection was given four and one-half months after the operation. By that time the normal adrenal had been so stimulated by the additional labor imposed upon it that—aided perhaps by a collateral nerve-supply—it assumed the functions of both. Hence "there was an equal amount of lacrymal secretion in both eyes."

Assuming, then, that pilocarpine increased functional activity by enhancing local blood-pressure, which means more oxidizing plasma, and that the current typified the nerve-impulse, thus reproducing the active process that prevails in muscular functions, why should removal of the stellate ganglion markedly influence these effects? This involves the consideration of an important feature of the problem: *i.e.*, the origin of the impulse-waves to which we ascribe all the functions credited to the motor nerves, the sympathetic nerves, and the vasomotor nerves. To simplify matters, however, we will not trace the various nervous organs involved to their primary source, but only to their common meeting-place: *i.e.*, the medulla.

That this will suffice for the time being is well shown by experimental transverse sections of the structure, on the one hand, and simultaneous electrical stimulation of a peripheral

nerve, on the other. The reflex contraction produced in the vessels and the consequent rise of blood-pressure continue as long as the downward reduction of tissues by slicing progresses. As soon as the medulla is reached, however, signs of impaired activity appear: the blood-pressure becomes reduced, and gradually sinks to naught when a certain level is reached. Again, as is well known, division of the spinal cord immediately below the medulla is followed by dilation of the *entire* vascular system and a corresponding decline of the blood-pressure, while electrical stimulation of the cut surface of the lower segment is followed by general vascular contraction and a proportionate rise in the blood-pressure. We can safely assume, therefore, that removal of the stellate ganglion modified the effects of the poison, because it severed the connection between the terminal fibers in the lacrymal glands acting as vasoconstrictors, and their center in the medulla.

That it was only under the influence of excessive stimulation that the lacrymal glands showed their abnormal condition, however, is shown by the fact that in each of the three animals the organ on the operated side remained normal when not under the influence of the drug. And yet it would seem as if, the vessels having lost on that side their tonic contraction, some morbid evidence of this fact should appear. That it did not suggests that the sympathetic fibers are not distributed to the intraglandular vessels, but to the arteries and arterioles outside the gland, as in the case of the muscular fibers. Indeed, the vessels that are supplied with muscular walls, small arteries, and arterioles, and to which nerve-filaments are distributed, do not penetrate the glandules; diminutive capillaries alone reach them, along with fine nervous filaments. We thus have two distinct kinds of vascular supply connected with the gland: an internal system of capillaries, the walls of which, as elsewhere, contain no muscular fibers, and an external system of small arteries or arterioles which are supplied with a muscular coat. The fact that the gland on the operated side remained normal in the experimental animals, unless submitted to great vascular pressure, coupled with the principle submitted in the earlier chapters—*i.e.*, that vessels supplied with a muscular coat are antagonistic to capil-

laries in contraction and dilation—will now furnish us a clue to the functional mechanism of the organ.

It seems clear that if, notwithstanding the dilation of the vessels, the glandules did not become active it was because these vessels were not directly connected with them; in other words, because the secretory part of the organ was not situated in the direct pathway of the blood-stream. Under these conditions a gland would receive its blood-supply through an arterial loop and only become active when the main channel would be *constricted.* It would bear the same relation to the main blood-path that a side-track bears to the main track of a railroad. Unused, the side-track typifies the passive state; used, it represents the active state, the latter being assumed when the main track is blocked. Unusual dilation of the main blood-path, under these circumstances, would deplete the gland, if it bore any influence upon it at all; a small dose of pilocarpine, while causing lacrymation in the normal gland, would hardly overcome the excessive vascular dilation of the one on the operated side; a large dose, on the contrary, by increasing *general* vascular pressure, would so engorge the weakened vessels as to cause excessive lacrymation on the corresponding side, as observed in Onuf and Collins's first two animals.

The functional mechanism just referred to can be studied with more precision in the next subject to be analyzed.

The Salivary Glands.—When the effects of increased blood-supply on the functional activity were reviewed, we saw that when the chorda tympani was stimulated after section the submaxillary gland assumed marked activity; its vessels became greatly enlarged, and its main trunk, which gave passage to blackish blood before the experiment, remained as red as arterial blood as long as the chorda tympani was stimulated. Evidently this nerve is the intermediary of the gland's functions, and Professor Foster is inclined to even exclude the sympathetic as an efferent nerve and to assign all the attributes of such a nerve to the chorda tympani. Even from our standpoint this view is tenable, since it not only distributes filaments into the gland, but another besides, which reaches the organ "along the small arteries" distributed to it. To the

former may be ascribed the rôle of motor nerve, which conveys impulse-waves that incite the gland to activity and govern the latter, while the part of vasodilator would be fulfilled by the vascular fibers. We thus require nothing more to complete the gland's functional mechanism.

Still, it is difficult to concede that the copious supply of sympathetic fibers along the branches of the facial and lingual that penetrate the organ should hold no place in the active process, since their exclusion as efferent nerves simultaneously eliminates them from the latter. If their influence on the parotid gland can be taken as a standard, however, whatever part they play, though perhaps not directly connected with active function, must be directly concerned with the structural integrity of the organ. Thus, Onuf and Collins state that "when the parotid gland is thrown into an intense activity by the cerebral secretory nerve so that it secretes from twelve to thirteen cubic centimeters of saliva, the secretion scarcely differs in its microscopical appearance from that of the gland in a state of rest. If, on the other hand, it has secreted from two to three cubic centimeters of saliva under the influence of the sympathetic nerve, the character of the cells is changed to such a degree that one thinks he has to deal with a completely new organ." They also refer to the experiments of von Wittich, which showed that "excitation of the cervical sympathetic nerve remained without effect upon the secretion of the parotid gland, if the facial nerve of the same side had been torn out from the cranial cavity either immediately or some days before." All this suggests that the sympathetic fibers, as is probably the case with the lacrymal glands, are not distributed directly to the glandular elements: a view emphasized by the experimental observations of Heidenhain, which showed that the secretion obtained by excitation of the sympathetic nerve (in dogs or rabbits) was very scarce. That similar experiments would be followed by corresponding results in the case of the submaxillary glands is very probable, inasmuch as their functions, nervous and vascular supply, and general histological structure are similar to those of the parotids.

Foster's belief that the chorda tympani is practically the

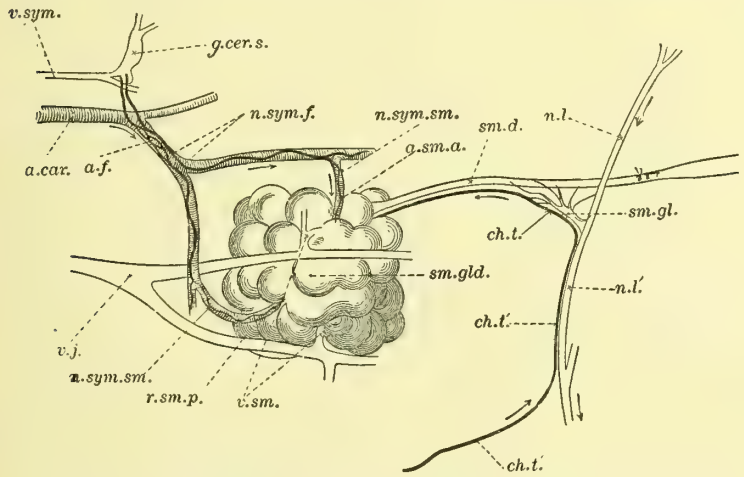
sole efferent nerve of the submaxillary gland is therefore justified. Indeed, using his words: "Section of that nerve, either where the fibers pass from the lingual nerve and the submaxillary ganglion to the gland or where it runs in the same sheath as the lingual, or in any part of its course from the main facial trunk to the lingual, puts an end, as far as we know, to the possibility of any flow being excited by stimuli applied to the sensory nerves or to the sentient surfaces of the mouth or of other parts of the body." Referring to the fibers of the chorda tympani when this nerve reaches the gland, he says: "The fibers may be traced into the gland for some distance, but, as we have said, *their ultimate ending has not yet been definitely made out.*[10] Along its whole course up to the gland, the fibers of the chorda are very fine medullated fibers, but they lose their medulla in the gland. The other set of nerve-fibers reaches the gland along the small arteries of the gland."

If the annexed engraving, taken from Professor Foster's work, is carefully examined, however, it will become apparent that the circulation of the organ and the sympathetic fibers are intimately associated. The arteries are terminal subdivisions of the carotid, while the veins are primary channels that ultimately lead to the jugular: features which emphasize their functional importance. Over these are entwined sympathetic fibers from the superior cervical ganglion, which fibers are inclosed in a common sheath with the main sensory nerve present, the vagus: further evidence that they must, in a measure, govern the quantity of blood distributed to the organ. In fact, this association with the vagus, sufficiently intimate "to form what appears to be a single trunk," almost imposes the deduction that the arterial branches of the latter nerve transmit the impulse-waves that emanate from the centers upon which the "nervousness" of speakers, actors, etc., depends as to the condition of "dry-mouth," or temporary xerostomia, so frequently observed. Such an inosculation is not due to mere hazard; it strongly suggests that the sympathetic fibers form part of the mechanism through which the intraglandular blood-pressure of the organ is governed: a fact

[10] All italics are our own.

confirmed by further inquiry into the mechanical attributes of the organ.

Admitting, for the time being, that, as implied by the word "vasodilator," the chorda tympani can dilate the walls of the vessels to which its fibers are distributed, how could it do so and so remarkably increase the blood-flow without the co-operation of the sympathetic fibers? An answer—based on



DIAGRAMMATIC REPRESENTATION OF THE SUBMAXILLARY GLAND OF THE DOG, WITH ITS NERVES AND BLOOD-VESSELS.

"The dissection has been on an animal lying on its back, but since all the parts shown in the figure cannot be seen from any one point of view, the figure does not give the exact anatomical relations of the several structures.

"*sm.gld.*, The submaxillary gland, into the duct (*sm.d.*) of which a cannula has been tied. The sublingual gland and duct are now shown. *n.l.*, *n.l.'*, The lingual branch of the fifth nerve; the part *n.l.* is going to the tongue. *ch.t.*, *ch.t.''*, The chorda tympani. The part *ch.t.''* is proceeding from the facial nerve; at *ch.t.'* it becomes conjoined with the lingual (*n.l.'*), and afterward diverging passes as *ch.t.* to the gland along the duct; the continuation of the nerve in company with the lingual (*n.t.*) is not shown. *sm.gl.*, The submaxillary ganglion, with its several roots. *a.car.*, The carotid artery, two small branches of which (*a.sm.a.* and *r.sm.p.*) pass to the anterior and posterior parts of the gland. *v.sm.*, The anterior and posterior veins from the gland, falling into *v.j.*, the jugular vein. *v.sym.*, The conjoined vagus and sympathetic trunks. *g.cer.s.*, The upper cervical ganglion, two branches of which, forming a plexus (*a.f.*) over the facial artery, are distributed (*n.sym.sm.*) along the two glandular arteries to the anterior and posterior portions of the gland.

"The arrows indicate the direction taken by the nervous impulses during reflex stimulation of the gland. They ascend to the brain by the lingual and descend by the chorda tympani." (*Foster.*)

prevailing doctrines—at once suggests itself: When the gland is in the *passive* state, the fibers of the chorda tympani "block" the entrance of blood into the organ by causing constriction of the intraglandular arterial subdivisions before the capillaries are reached; when the gland is to assume the *active* state, they allow the "block" to relax and a correspondingly greater amount of blood to pass. Indeed, present teachings do not in any way grant constricting powers to the chorda tympani but *active* dilating properties: *i.e.*, it is thought to actually dilate the vessel by relaxing its muscular coat,—the foundation of the belief that vasodilators exist.

Is such a mechanical dilation of the arteries or arterioles distributed to the gland possible? The intraglandular supply is mainly composed of capillaries, which, of course, have no muscular coat. The smaller arteries or arterioles end as such soon after entering the organ; as the filaments of the chorda tympani follow the course of these vessels we may surmise that their terminal end-plates are attached to the muscle-fibers of the arterioles; but, to avoid any error on this score, we will consider that they end in the muscular layer of "the small arteries" to which Professor Foster refers. Unless we can ascribe to the nerve-endings themselves the lifting power required to relax the vessels, we must depend on some source of expansile elasticity such as that shown to exist in the vessels distributed to muscles, in the elastic festooned layer described by Ranvier. That the vessels are not mechanically disposed so as to forcibly dilate the vascular walls hardly needs mention. Nor does an elastic expansile lamina under the vascular layer exist in these vessels, which, besides their muscular coat, are only endowed with an internal endothelial layer and an external adventitious coat. From the standpoint of mechanics, therefore, there is nothing upon which active dilation of the vessels could depend. In the light of the views submitted in this work, therefore, and particularly since the sympathetic and the chorda tympani are merely considered as subdivisions of the one great motor system, we find ourselves obliged to account for the functions of the submaxillary gland with two vaso*constrictor* nerves (sympathetic and chorda tympani) and filaments of one of these as the transmitters of inciting and

regulating impulses. As the three sets of terminal nerves thus originate from the one general system, the same impulses must furthermore satisfy the needs of all three—as we ascertained was the case with muscles.

Before defining the manner in which we interpret the functional process, a few quotations from Professor Foster's work will serve to show that we are probably not on a wrong path. As to dual function of the chorda tympani, he says, referring to a series of experiments reviewed by him: "They further lead us to suppose that the chorda contains two sets of fibers, one of which we may call secretory fibers, acting directly on the secreting structures only; and the other, vasodilator fibers, acting on the blood-vessels only." Again, and what seems to us to be a striking indirect confirmation of our views: "When the chorda is stimulated, there pass down the nerve in addition to impulses affecting the blood-supply, impulses affecting directly the protoplasm of the secreting cells, and calling it into action, just as similar impulses call into action the contractility of the substance of a muscular fiber. Indeed, the two things, secreting activity and contracting activity, are very parallel."

The functional mechanism of the submaxillary gland, as we view it, is as follows:—

Some fibers of the chorda tympani are distributed to the secreting elements to excite and govern their metabolism; the remaining fibers of the same nerve are distributed to some of the glandular arterioles, but not to those which supply capillaries to the secreting elements. While the gland is in the passive state the blood flows equally through all arterioles.

When the gland is active, the chorda tympani constricts the arterioles to which it supplies fibers, and thus forces the bulk of the blood through the free arterioles and thence into the glandular capillaries.

The rapidity of the blood-flow through the organ is concurrently increased through sympathetic constriction of the extra-glandular arterial branches functionally connected with the gland.

The effect of stimulation of the chorda tympani as noted by Professor Foster now seems clear: "The small arteries of the gland become very much dilated, and the whole gland

becomes flushed." From our point of view, this applies to the arteries deprived of chorda-tympani fibers, since those supplied with these fibers are contracted and hidden to a greater degree than before. "Before stimulation the blood trickles out in a thin, slow stream of a dark, venous color; during stimulation the blood rushes out in a full stream, often with a distinct pulsation." Even during excessive glandular activity, the general circulation remains unaffected; hence some local means must intervene to greatly increase the blood-flow; a slight increase of speed is doubtless afforded by the shifting of the blood-stream into the glandular arterioles, but the passage of the blood through the capillaries, glandular elements, etc., very soon annuls this gain. Indeed, powerful pressure is required to overcome these obstacles; hence the presence of vasoconstrictor "sympathetic" fibers around the arteries, to reduce their lumen and thus increase the *vis a tergo* power of the blood-stream. These arteries being outside the gland, as compared to those constricted by the chorda tympani, we will call them *"extrinsic"* constrictor fibers in contradistinction to those of the latter nerve, which we will call *"intrinsic."* The same arrangement prevails in muscles to increase the general flow of blood through them when incited to activity, and in addition to the fibers distributed to the arterioles just before these give off capillaries to the muscle-fibers.

Sudoriferous Glands.—The confusion that the literature upon the secretion of sweat so plainly indicates in respect to the mechanism of this function is easily accounted for when we recall the important part taken in the process by practically unknown organs: *i.e.*, the adrenals and their consorts, the anterior pituitary and the thyroid. We have seen that free sweating attended the erethic stage of exophthalmic goiter, and, furthermore, have ascertained that lacrymation could be caused by pilocarpine as a result of the increase of blood-pressure this alkaloid was able to produce. If we now recall the fact that the sweating caused by it is attended with peripheral hyperæmia,—*i.e.*, flushing,—the link with the first stage of exophthalmic goiter, also essentially due to suprarenal overactivity, along with its physiological sequelæ (contracted central vascular trunks, intense peripheral engorgement of the

capillaries), will appear. This process implicates, however, the participation of a certain—though limited—degree of mechanical force, along with the enhanced metabolism brought about by the quantity of oxidizing plasma present in the active local process induced.

A brief summary of the histology of this system is necessary, however, to illustrate the various features to be studied. The capillaries form a close net-work around the coiled tubes, and reach down to an extremely thin basement membrane, which, in turn, surrounds the layer of muscular fibers that coil around these tubes. An important feature of this muscular layer,—which is only separated from the cavity or lumen of the tube by the secreting epithelial cells and their endothelial lining,—however, is that its ribbon-like fibers are spirally wrapped round the tube, and in such a manner as to leave a gap between their border, throughout their whole length. Not only, therefore, is the thin basement membrane thus enabled to reach the secreting cells through the gaps, but the former actually project through the latter so as to touch the membrane. Furthermore, the projecting cells are so related to one another as to form canaliculi-like spaces, which extend from the capillary-covered membrane completely through to the lumen of the tube (Ranvier). The mechanism of the sweat-secretion is not difficult to understand if these facts are borne in mind: Contraction of the muscle not only shortens the tube longitudinally, but causes it to contract when the oxidizing plasma in the capillaries is increased through peripheral vascular engorgement, whether this be due to constriction of the arterioles from which the capillaries arise or to contraction of the central vascular trunks. Both sources of peripheral blood-pressure act in precisely the same manner: They engorge the tubular capillaries, excite the functional metabolism of the underlying muscles, and force the glandular secretion into the tubular lumen and up along the duct to the cutaneous surface. We can readily understand, therefore, why pilocarpine should, by stimulating the anterior pituitary and through it the adrenals, give rise to profuse sweating.

The experiments of Luchsinger, undertaken with other phases of the problem in view, may also be used in this con-

nection: *i.e.*, to illustrate the independence of the process from the nerve-centers, when sweating is *induced.* This physiologist cut the sciatic nerve of a young cat, then injected pilocarpine. Sweating from the four paws occurred, the operation having in no way interfered with the result. We have seen that removal of the stellate ganglion in cats was followed by loss of vascular tonicity in the head-supply, but it likewise does so in the upper extremities. We also know that the adrenal on the normal side, and probably collateral nerves connected with that on the operated side, compensate, in a measure, for the primarily isolated organ. Onuf and Collins removed the left stellate ganglion of a cat and three months later injected pilocarpine. About ten minutes after the injection both front paws were sweating; the left, however, less than the right; six hours later all paws were still somewhat moist. In another animal "instillation of a few drops of a 2-per-cent. solution of pilocarpine into each eye produced sweating of all paws, apparently no less of the forepaw of the side (right) on which the stellate ganglion had been removed four and one-half months previously." We are evidently dealing with a *general* functional mechanism, the most active part of which is ascribable to the adrenals.

Another side of the question may be introduced by quoting a passage from the paragraph immediately after that just referred to. Alluding to the first cat (No. 2 in their series), from which the left stellate ganglion had been removed, Onuf and Collins say: "But yet we had to note the paradoxical fact that, when, on a later occasion, we began the etherization of cat No. 2 in order to perform another operation, the struggles of the animal against being etherized produced considerable sweating of all paws except the left forepaw, which remained perfectly dry." We are no longer dealing here with *induced* diaphoresis, but with the purely physiological form of sweating,—that due to excessive muscular activity,—and involving primarily, therefore, active participation of the nervous system. In the induced form, on the other hand, sweating was incited inordinately through overaction of the adrenals and through stimulation of the medullary centers. Yet there is also involved in the process much of the same

mechanical pressure present in induced sweating,—that to which reference was made when excessive muscular activity was studied: *i.e.*, increased cardiac activity. When pilocarpine is given in sufficient doses to produce marked diaphoresis, the heart-beat is increased in power, but lowered as to rhythm. During the sweating from violent physical exercise the heart-beats are increased in power, but *quickened* in rhythm. Hence there is a more or less marked loss of balance between the various functional features that contribute to the general process when induced sweating occurs, while there is perfect balance in all these when diaphoresis occurs physiologically as it does during unusual physical exercise. It is only when the centers are able to adequately utilize the two subdivisions of the *single* efferent nerve that supplies glands *concurrently* with perfect functional activity of the suprarenal system, that normal—*i.e.*, physiological—diaphoresis may be said to occur.

In Onuf and Collins's cat No. 2 physiological sweating supervened; but the centers could no longer transmit efferent impulses to the secretion-exciting fibers nor to the arterioles from which the tubular capillaries sprung. The functional process therefore failed. Had it received the aid of the powerful blood-pressure that pilocarpine procured through the suprarenal overactivity, however, it would not have fallen short. Nor did it when, in this same animal, the alkaloid was put to the test.

In analyzing the manner in which the nervous supply of the sweat-glands originates and its relationship with the tubuli we will test the following postulate, suggested by our study of the innervation of the muscles and submaxillary glands:—

1. All efferent nerves to the periphery and to voluntary muscles are subdivisions of the one great motor system.

2. There are but two divisions of the great motor system: (1) the "vasoconstrictor" nerves, and (2) the "excito-regulator" nerves, which incite and govern the metabolism of the glandular elements.

In moribund cats, while the heart-action is growing weaker, sweating of the toe-pads occurs; and if these are not pigmented they become pale and exsanguine (M. Duval). This corresponds with the profuse sweating of death-agony in human beings, attended, of course, with great pallor or lividity. We

may recall the fact that several toxic drugs reviewed in one of our earlier chapters—nicotine, for instance—produced identical effects. We have also seen that sweating is a marked symptom of exophthalmic goiter during its cachectic stage, and, indeed, of many diseases when marasmus prevails. In all of these pallor of the surface and of the mucous membranes points to the prevailing mechanical feature,—*i.e.*, engorgement of the internal vascular trunks,—and therefore to suprarenal insufficiency. In the sweat-glands proper the opposite condition to that observed after the use of pilocarpine obtains: *The functional metabolism of the acini and of the tubular muscles is reduced; the canaliculi between their edges are unusually patent; the entire structure of the organ is relaxed and allows the secretion to exude more freely through its elements.*

How is this impairment of the sudoriparous functions induced by suprarenal insufficiency? Section of the cervical sympathetic in the horse is followed by profuse sweating on the corresponding side of the head, owing to the relaxation of the vessels: *i.e.*, to loss of their tonic contraction. We also know that section of the spinal cord below the medulla is followed by the same loss of tonic vascular contraction throughout the entire organism: experimental data which again refer us to the medulla as the origin (apparent) of the impulse-waves by means of which the sympathetic fibers govern the vascular tone of the arteries and arterioles from which the capillaries distributed to the sweat-glands are derived. We are not only dealing, therefore, with a mechanical phenomenon based upon reduced peripheral blood-pressure brought on by the central engorgement, but with one in which the normal functional activity of the centers is lowered just as it is lowered when the cord is cut below the medulla—the scalpel being replaced by a reduction of its blood-supply. We, therefore, have two interdependent causes for the relaxation of the peripheral blood-channels, viz.: accumulation of the blood in the central vascular trunks and loss of tonic contraction of the peripheral vessels through the lowered potentiality of the impulse-waves transmitted to the latter *via* their sympathetic filaments.

We have expressed the belief that there were but two

divisions of the great motor system, the vasoconstrictor and the excito-regulator nerves, and, furthermore, that all efferent nerves were subdivisions of this system. If the sympathetic nerves *are* the vasoconstrictor nerves, we are therefore bound to account for any functional phenomenon witnessed attributable to impulse-waves to the only remaining division: that which we have termed "excito-regulator."

The question as to whether such excretory nerves exist at all has been the source of considerable controversy. Vulpian recognized the existence of "sweat-exciting fibers," but he was logically led to conclude, in order to account for the fluctuations of activity actually witnessed experimentally and during morbid states, that "secretion-moderating fibers" likewise existed. Foster, referring to both these nervous elements, says: "Though the idea of a double nervous mechanism, augmenting and inhibitory, governing the activity of the sweat-glands, is a tempting one, there are at present no satisfactory reasons for adopting it." We have just seen that the amount of blood allowed to reach the sudoriferous glands—or, to speak more correctly in accordance with our views, the amount of blood-*plasma* allowed to reach the secreting structures—greatly influenced their activity; we might, therefore, consider the sympathetic fibers as the "moderating fibers." Still, they not only moderate the intensity of the process, but also likewise increase it. The same line of argument applies to the term "sweat-exciting fibers," and we are, therefore, obliged to refrain from using these terms, much as we are desirous of preserving all we can of the nomenclature introduced by such investigators as Vulpian. Indeed, both peripheral subdivisions belonging, from our standpoint, to a single system, we cannot attribute to one subdivision a *physiological* governing influence over the other. As we view it, fluctuations affect both divisions equally, the one flow of impulse-waves governing all functions under their domination, and we look upon any variation in this functional parallelism, balance, or equipoise as pathogenic, whatever be its cause.

That sympathetic fibers are distributed to these organs is a recognized fact. All the experimental evidence adduced —section of the sciatic, including its sympathetic fibers; Vul-

pian's, Luchsinger's, Onuf and Collins's experimental removal of portions of the sympathetic ganglionic chain—attests to this. The latter authors state that "some writers (Nawrocki and Luchsinger, and Langley) go so far as to say that all sweat-fibers destined for the limbs are derived indirectly—*i.e.*, through the intermediation of the sympathetic nerve—from the spinal cord." That the upper extremities and head are also supplied with them has been emphasized in the foregoing pages. We are warranted, therefore, in ascribing to these fibers the functions of one of our divisions, the "vasoconstrictor," for the entire sudoriferous glandular system. Through these vasoconstrictors the blood-plasma is ultimately brought to the secreting structures, including the spiral muscles, furnishing them with working energy and with the constituents, water included, of the excretion itself.

If "excito-regulator" nerves exist, to which of the component parts of the sweat-glands are they distributed? The vasoconstrictor fibers, judging from their rôle in the voluntary muscular system, may be considered as extrinsic to the sweat-system itself, since they can, by constricting arterioles long before the organ is reached by capillaries, regulate not only the amount of blood allowed within the secreting elements themselves, but also in the spiral muscles around the tubes. We may, therefore, consider the vasoconstrictors as fully accounted for topographically, and also as regards the nature of their duties, which coincide with those found to be theirs in the submaxillary gland. The "excito-regulator" nerves, therefore, must include within their area of influence the remaining inherent factors of the local functional process: *i.e.*, contraction of the spiral muscles and metabolism of the epithelial secreting cells. It is evident that considerable analogy exists between sudoriferous glands and salivary glands. In the submaxillary gland we also had, besides the vasoconstrictors, to account for two functions through the one nerve, the chorda tympani, one subdivision of which went to muscular fibers (those of the "blocking" vessels) and the other to the glandular elements. That the excito-regulator division may dichotomize —each of the subdivisions being called upon to excite and regulate a different, though functionally related, structure— is evident.

Can we conclude that such a system prevails in the sweat-glands? Each glomerule of coiled tubes is surrounded by a plexus of non-medullated fibers containing a number of nerve-cells, while analogy renders it self-evident that the glandular muscles must, as all muscles do, receive their stimulus through nerve-filaments. The fact that they are of the smooth variety does not modify this relationship, since Tschiriew showed that "no essential morphological difference exists between nerve-endings in striated muscles and those in smooth muscles." Dejerine[11] also states that "all nerves end in the form of free arborizations, and the different modes of contraction of the various kinds of muscle in no way depend upon the form of their nerve-terminations." Finally, Onuf and Collins remark: "For the sweat-glands of the head even Luchsinger admits both a sympathetic (fibers of the cervical sympathetic nerve) and a direct non-sympathetic nerve-supply, the latter being furnished either by the spinal cord or the medulla." We have seen that this also applies to the rest of the organism. Reduced to its simplest expression, therefore, the functional mechanism of the sweat-glands would be as follows:—

The efferent nerves of the sweat-glands are two in number, both divisions of the general motor system. One of these, the "intrinsic vasoconstrictor," is distributed to the glandular arterioles; the other, the "excito-regulator," subdivides into two branches, one of which is distributed to the spiral muscle of the tube and its coils, and the other to the secreting elements.

When a sweat-gland is active, the "intrinsic vasoconstrictor" nerve constricts the arterioles and thus forces more blood into the glandular capillaries to supply sweat-constituents and work-energy; one subdivision of the "excito-regulator" nerve incites and governs the activity of the secreting elements, while the other causes axial and centripetal contraction of the spiral muscle around the coiled and straight tube.

The rapidity of the blood-flow through the organ is concurrently increased through the "extrinsic vasoconstrictor" nerves of the extraglandular arterioles.

All this being carried on through the agency of a single flow of impulses, the several elements of the process undergo

[11] Dejerine: "Anatomie des Centres Nerveux," p. 229, 1895.

functional fluctuations simultaneously, thus rendering antagonistic augmentor and inhibitor nerves unnecessary. Nor can we deem applicable the term "vasomotor" nerves to regulate the blood-supply, since it implies active vasodilation besides vasoconstriction. We have seen that "vasodilation" could not be active; hence "vasoconstrictor" alone denotes the true function of such a nerve, vasodilation being either passive or indirect. The term "secretory" appears as faulty from our standpoint, since it also suggests that the nerve possesses, besides its own attributes,—*i.e.*, to excite and regulate glandular activity,—the power to supply the energy required to sustain the process, which is not the case.

That the foregoing views are sound is suggested by the facility with which various familiar experiments are accounted for. "If in the cat," says Foster, "the peripheral stump of the divided sciatic nerve be stimulated with the interrupted current, drops of sweat may readily be observed to gather on the hairless soles of the foot on that side." The sciatic, as we view it, supplies all the nerve-impulses of the organ; stimulation will, therefore, furnish all the energy required for the entire process. Again, he states: "The sweating is not due to any increase of blood-supply, for it may be observed when the cutaneous vessels are thrown into a state of constriction by the stimulus. . . ." We have seen that this very constriction is an important feature of the process, as we understand it, since it insures rapid *vis a tergo* motion and increased energy. Continuing the sentence, he adds: ". . . or even when the aorta or crural artery is clamped previous to the stimulating of the sciatic nerve of a recently amputated leg." Even these factors should not prevent diaphoresis, if, as we contend, the motor nerve—the sciatic, in this case—contains both sets of functional fibers. The motor apparatus being thus complete, the amputated limb is thus far better able to respond normally to an artificial stimulus than would a system embodying mutually antagonistic nerves, such as that now thought to prevail. "Moreover," says Professor Foster, "when atropine has been injected, the stimulation produces no sweat, though vasomotor effects follow as usual." It is evident that the drug caused this by inducing adrenal insufficiency, thus

dilating the central vascular trunks and depleting the peripheral capillaries. While the other part of the sweat-gland mechanism may, therefore, act normally, the impulse-waves lose their influence. Finally, he remarks: "The analogy between the sweat-glands of the foot and such a gland as the submaxillary is, in fact, very close; . . ." so close, we may add, that the existence of a common source of energy, a common channel for its transmission, and a common peripheral mechanism can scarcely be doubted.

Mammary Glands.—Foster refers to the influence of the nervous system upon the functions of the mammary glands in the following words: "That both the secretion and ejection of milk are under the control of the nervous system is shown by common experience, but the exact nervous mechanism has not yet been fully worked out. While the erection of the nipple ceases when the spinal nerves which supply the breast are divided, the secretion continues, and is not arrested even when the sympathetic as well as the spinal nerves are cut."

The nerves that supply these organs and the skin covering them are the intercostals from the second to the sixth, inclusive; the thoracic branches of the brachial plexus; and the descending branches of the cervical plexus, while sympathetic filaments accompany all blood-vessels.

In this analysis we will, in a measure, cover two subjects, since the mammary secretion is carried on in a manner similar to that which prevails in sebaceous glands. The functional process in the latter and the similarity referred to are well illustrated in the following quotations from the work of W. Roger Williams.[12] Referring to the sebaceous glands, this author says: "Within the *membrana propria* of its secretory part we find a stratum of small, irregularly-shaped *epithelial cells*, each with a large nucleus (Fig. 1, *b*). The cells of this region are constantly proliferating, and, as the products of the process gradually shift *toward the duct*, they become changed and gradually form the secretion." If the words that we have italicized are placed in immediate sequence, they will be found to exactly describe the histological arrangement of the sweat-tubes from the delicate membrane to the lumen. "The steps

[12] W. Roger Williams: "Diseases of the Breast," London, 1894.

of the process are as follows: The cells next the marginal cells (Fig. 1, *b*) increase in size and their nuclei dwindle. As they approach the center of the acinus their nuclei disappear, and the cells become distended with granules and oil-globules. Finally they burst and their *débris* forms the secretion, which is discharged." This also coincides with the manner in which sudoriferous glands produce their secretion.

"Lactation is the outcome of a similar process," continues Mr. Williams. "Milk must, therefore, be regarded as the product of the deliquescence of successive degenerations of epithelial cells which are destroyed in this process and replaced by relays of new cells derived by division from other still active

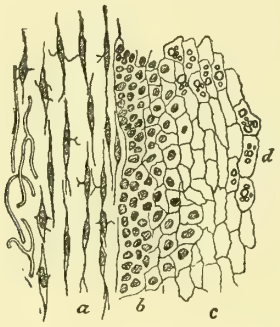


FIG. 1.—HISTOLOGICAL SECTION OF THE WALL OF A SEBACEOUS CYST. (*Cornil and Ranvier.*)

a, Fibrous stratum with connective tissue corpuscles. *b*, Marginal stratum. *c*, Hornifying cells. *d*, Sebaceous cells.

epithelial cells of the part. Thus we see that growth, development, and secretion are but slightly varied manifestations of cellular activity finding expression in different ways." . . . "The complete degree of mammary function that eventuates in lactation is only attained periodically, and the process is always gradual. The following is a brief account of Creighton's description of it: Subsidence of the function goes hand in hand with undoing of structure, and revival of the function with the building up of structure. Variations of intensity in the secretory force are measured by its products which correspond to changing aspects of the secreting acini. The beginning of the rising function coincides with the be-

ginning of pregnancy, and the process occupies the entire period of gestation. During the intervals between its periods of functional activity the breast remains in a quiescent functionless state: the *resting* stage. In this condition the gland is shrunken and surrounded by a considerable quantity of fibro-fatty tissue. The acini are shriveled up. On microscopical examination of sections of the gland in this stage (Fig. 2) each acinus appears as an alveolar space bounded by a thin layer of fibrous tissue, denuded of epithelium. Its contents are irregularly-arranged, polymorphic, epithelial cells, with large nuclei and scanty surrounding protoplasm. . . .

"During the *rising* function the size of the acini grad-

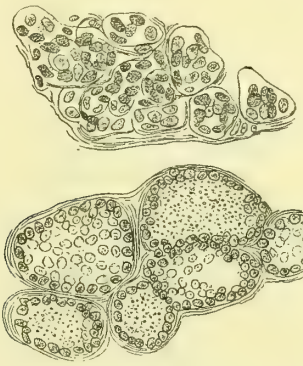


FIG. 2.

FIG. 3.

THE MAMMARY LOBULE NEAR THE RESTING STAGE (UPPER) AND DURING FUNCTIONAL ACTIVITY. (*Creighton.*)

ually increases from that of the resting stage. The cells increase in number and size and acquire more protoplasm. They gradually arrange themselves so as to form a lining membrane for the wall of the acinus (Fig. 3), which, as lactation approaches, is converted into a regular mosaic. The cells become granular, irregularly shaped, excavated, and vacuolated, secreting granular and mucous fluids. The milk of the first few days is always somewhat crude, containing colostrum-cells, which are the last of the long series of secretory products thrown off during the period of rising function.

"The fully-expanded acinus (Fig. 4) in a state of active secretion is at least four times as large as that of the resting

stage. Its contained cells are much more numerous than at any other period, and they form a perfect mosaic, lining the membrana propria. Each cell is flattened and of polyhedric shape, and has a large nucleus surrounded by a broad zone of protoplasm.

"During the period of subsiding function the organ gradually reverts to the resting stage through the converse series of changes. In this process the cells pass through a succession of transformations, from the forms characteristic of the perfect mosaic of lactation to those peculiar to the various stages of the subsiding process. These changes are accompanied by constant destruction and renewal of the participating cells.

"With regard to the influence of the nervous system on

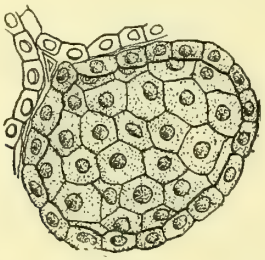


FIG. 4.—EXPANDED MAMMARY ACINUS, SHOWING THE ARRANGEMENT OF EPITHELIAL MOSAIC. (*Creighton.*)

the mammary secretion, most of those who have studied the subject are agreed that the secretion of milk is not directly under its control. Laffont,[13] however, maintains that the mammæ possess *vasodilator* nerves which, *when stimulated*, cause augmentation of the quantity of milk secreted; but de Sinéty,[14] who has repeated his experiments, is unable to accept his conclusions."

The foregoing review not only indicates the important part cellular metabolism plays in the functions of the mammary glands, but also that the blood is an important source of active functional work. "The blood is the ultimate source

[13] Laffont: Comptes-Rendus de l'Académie des Sciences, vol. lxxxix, 1879.
[14] De Sinéty: Mémoires de la Société de Biologie, vol. i, 1879.

of milk," says Foster, "but it becomes milk only through the activity of the cell, and that activity consists largely in a metabolic manufacture by the cell, and in the cell, of the common things brought by the blood into the special things present in the milk. Experimental results tell the same tale." Another feature which it places on a solid footing when associated with Professor Foster's research, and one which we wish particularly to emphasize, is the identity of the liquid which holds the various constituents of milk in solution, viz.: blood-*plasma*. This is also suggested by a statement of M. Duval's, who, referring to the formation of cream, says: "The transparent portion that remains at the bottom of the vessel represents the plasma of the milk: that is to say, the milk without globules. We employ the word 'plasma' here to establish a parallelism between the analysis of milk and that of the blood. Skimmed milk corresponds to the liquor of the blood."

In the chapter on "Immunity" the true identity of blood-plasma, owing to its inherent oxidizing substance, its alexins, etc., as a prophylactic, and its rôle in this connection, will be further studied. But, bearing directly upon the question in point,—*i.e.*, the functional mechanism,—the presence of plasma in the milk forcibly indicates that an important vasoconstrictor system must exist in the mammary gland. In fact, that so careful an investigator as Laffont should have observed vasodilation further emphasizes this, and tends to indicate that a process similar to that described by us in our analysis of submaxillary functions must prevail,—*i.e.*, *indirect* vasodilation,—a fact sustained by the counter-experiments of an equally competent physiologist, de Sinéty, who was unable to find vasodilators *per se*. Laffont reached his deduction that vasodilation occurred by measuring the blood-pressure in the mammary artery of a bitch, during lactation, after severing the mammary nerve and stimulating the peripheral segment of the latter. Congestion of the gland and increase of milk-flow followed, but after cessation of the artificial stimulation the flow, though not arrested, was greatly reduced. This led Laffont to conclude inferentially that the mammary gland possessed typical vasodilators similar to those thought to exist in the submaxillary gland. We have shown that the phenomena upon which

such a deduction could be based, in respect to the latter organ, could be accounted for without vasodilators and that active dilation was a mechanical impossibility. Claude Bernard's own testimony to this is indirectly afforded by the fact that the "interference" or "inhibition" theory was introduced by him to account for vasodilation: the existence of which he was first—as he had been in the case of vasoconstriction—to demonstrate.

The various data reviewed seem to us, when considered collectively, to suggest modifications of generally accepted views. In the mammary gland the secreting apparatus is formed, we have seen, first, by an extremely thin basement membrane, and, second, by a single layer of epithelial secretory cells. The latter supply the milk-forming elements other than the liquid *per se*, which liquid responds to various tests of blood-plasma (Duval) and seems to replace the water secreted by the sweat, salivary, and lacrymal glands. In all three of the latter organs, however, the secreting structures are surrounded by a net-work of capillaries. That such is also the case in the mammary gland is evident, since Piersol,[15] referring to the glandular vessels, says: "From these vessels on the anterior surface of the organ branches penetrate into the glandular mass and pass between the lobules, giving off twigs which break up into capillaries inclosing the alveoli." A net-work of nerve-filaments are also traced to the glandular elements of salivary and sudoriferous glands: a feature also reproduced in the mammæ. Thus, Böhm and von Davidoff,[16] alluding to the terminations of the nerves in the mammary glands, recall that they have been studied by means of the methylene-blue method by Dmitrewsky, who found that "the terminal branches form epilamellar plexuses outside the basement membrane of the alveoli, from which fine nerve-branches pass through the basement membrane and end on the gland-cells in clusters of terminal granules united by fine filaments." They also state that "the vessels form capillary net-works surrounding the alveoli." The ducts when nearing the nipple have an outer

[15] Piersol: "Normal Histology," p. 241, seventh edition, 1900.

[16] Böhm and von Davidoff: "Text-book of Histology," translated by Huber, p. 361, 1900.

layer of cellular tissue containing a large number of elastic fibers and smooth muscular fibers which depart slightly from the axial line in direction, though insufficiently so to be termed "spiral" as in the case of the sweat-gland muscles. But, in the mammary gland, suckling, by creating a vacuum and causing elongation of the nipple, fulfills the function of the latter.

We thus have all the structural elements of the previously studied glands present in these. Their peripheral mechanisms should also correspond, however. As to the nervous supply, we have seen that dilation of arteries was found to be controlled by motor nerves, by Laffont, and that the presence of vasomotors was denied by de Sinéty. Hence, the vasodilation must be due to indirect action, especially since Laffont caused it by stimulating these nerves, precisely as Claude Bernard had done in the case of the submaxillary glands. The stimulation must, therefore, have caused this indirect vascular dilation in the manner described when the chorda tympani was in question: *i.e.*, by causing constriction of *some* of the glandular vessels. That this conception of the process is justified is further sustained by the experiments of Rohrig,[17] who found that a *motor* nerve, the external spermatic, supplied constrictor fibers to the glandular blood-vessels in the goat, and that division of *one branch* of this nerve, the lower, enhanced secretion (evidently due to relaxation of the vessels through loss of their normal stimulus), while stimulation of the peripheral end of this subdivision of the nerve decreased the secretion. This clearly suggests that, just as is the case in the submaxillary gland, each motor nerve of the mammary gland gives off two subdivisions: one evidently to the vascular walls, the other, as we have seen, to the glandular elements.

As to the sympathetic fibers, they are also stated by Roger Williams to "accompany the mammary blood-vessels"; and, as section of a sympathetic nerve is always followed by dilation of the arteries, they can only act as vasoconstrictors here as elsewhere. That all efferent fibers distributed to the glandular elements and to the blood-vessels originate from the general motor system is evident when their relationship with

[17] Rohrig: Virchow's Archiv, vol. lxvii, 1876.

the cord, and particularly the results of section immediately below the medulla, are recalled. That a single stream of impulses from the cerebral centers can sustain the entire function —that is to say, that part of it under nervous control—scarcely needs, under these conditions, to be emphasized.

An important characteristic of the functions of the mammary glands, however, is that their dependence upon their nervous supply is not as great as is the case with other organs. This is readily accounted for when the identity of the liquid portion of milk is realized. The blood-plasma must undergo but little change during its conversion into milk-plasma; indeed, it is probably merely filtered through the membrana propria and the epithelial layer of cells in the lobules and thus becomes charged with their products. Leucocytes are the main source of the latter; Kadkin[18] found them both in the epithelial lining and alveolar cavities, "wherein disintegration of their nuclei supplies the milk with a proportion of its nuclein, the remaining amount of the latter being furnished by the epithelial cells." These bodies and the oxidizing substance of the blood-plasma not only transfer to the milk their immunizing qualities, but the oxidizing substance is itself a source of functional energy through which leucocytes and epithelial cells are caused to endow the milk with its nutritive principles. Much of the organ's work is therefore automatic.

While "the secretion continues and is not arrested even when the sympathetic as well as the spinal nerves are cut," control experiments soon show that, as was the case with Laffont's animal, the flow, though not arrested, is reduced even when only one set of nerves is cut. This indicates, when considered along with the fact that stimulation of the mammary end of the nerve increases the gland's activity, that the nervous supply must not be disregarded, and it also suggests that the sharp line drawn between "active" and "passive" activity, in the case of other organs, and which mainly depends upon nerve-impulses to secreting structures and vascular walls, is scarcely applicable here. Indeed, we are doubtless dealing with mere fluctuations of activity, called forth, during lacta-

[18] Kadkin: Inaugural Dissertation, 1890.

tion, by afferent impulses to the motor centers: a feature which the rapid formation of milk after nursing and the influence of emotions upon its flow suggest. In framing our summary of the functional mechanism of the mammary gland, therefore, it is not the difference between active and passive activity that we have in mind, but the manner in which fluctuations of activity are brought about. The actual process involved, even here, however, is primarily a mechanical one, since filtration of the blood-plasma into the secreting elements represents no mean expense of force. As blood-pressure totally independent of the normal systemic pressure must account for this, we are relegated to the vessel-walls and their nerve-supply as the intermediaries through which this is carried out.

Fluctuations in the functional activity of the mammary gland during lactation are brought about, if our views are well founded, in the following manner:—

Each of the motor nerves distributed to the mammary glands divides into two main branches. One branch, the "extrinsic vasoconstrictor" (ex-sympathetic), is distributed to the arteries outside the secreting structures. The other branch, the excito-regulator, subdivides into two branches; one of these, the "excitor," supplies fibers to the acini; the other, the "intrinsic constrictor," sends fibers to the glandular arterioles, but not to those which supply capillaries to the secreting elements.

During exacerbations of activity the branches distributed to the arterioles, the "intrinsic constrictors," constrict the latter, thus forcing the bulk of the blood through the free arterioles and thence into the capillaries of the secreting acini, while the "excitor" branch excites and governs the metabolism of the acini.

The rapidity of the blood-flow through the intrinsic blood-supply—arterioles, capillaries—and through the secretory elements, is concurrently augmented through increased contraction of the extralobular mammary arteries by the "extrinsic vasoconstrictor" (sympathetic) branches distributed to them.

General Conclusions as to the Mechanism of Functional Activity.—A number of general questions have been referred to in this chapter the discussion of which has to be

continued in the next, but the following deductions regarding the several organs the physiology of which has been analyzed appear warranted:—

1. The sympathetic system is structurally a part of the general cerebro-spinal motor system, and is endowed with no function other than that appertaining to the motor system: i.e., to transmit efferent impulses.

2. All efferent nerves distributed to the voluntary muscles, to the salivary, mammary, and cutaneous glands, are subdivisions of the general cerebro-spinal motor system.

3. The general motor nerves distributed to the organs above mentioned divide, when near their destination, into two branches: (1) an "extrinsic vasoconstrictor" branch, which supplies filaments to the arteries outside the contractile or secretory structures of the organ concerned, and increases the speed of the blood-flow through the latter during activity by reducing the caliber of these arteries; (2) an "excito-regulator" branch, which supplies the intrinsic structures of the organ and governs their functional activity.

4. In voluntary muscles and in the salivary, mammary, and cutaneous glands there are two sets of intrinsic arterioles: (1) a set which supplies capillaries to the contractile or secretory elements; (2) a set that does not, but, instead, crosses over to the venules before the contractile or secretory elements are reached.

5. In the glands mentioned the excito-regulator branch subdivides into two branches: one of these, the "excitor," supplies filaments to the secretory elements and excites them to activity; the other, the "intrinsic constrictor," is distributed to the intrinsic arterioles that do not supply the secretory structures with capillaries, constricts them during activity, and thus increases the blood-flow through those that do supply capillaries to the secretory structures.

6. In muscles the excito-regulator branch also subdivides into two branches: one of these, the "excitor," supplies filaments to the muscle-fibers and excites them to activity; the other, the "intrinsic constrictor," is distributed to the muscular arterioles that do not supply the muscular fibers with capillaries, constricts them during muscular contraction, and thus increases the blood-flow through those that do supply capillaries to the contractile elements.

7. As all the nervous subdivisions referred to, including the

subbranches and terminal filaments, originate from nerves derived from the general cerebro-spinal motor system, a single stream of efferent impulse-waves excites and regulates the functional activity of the organs concerned by simultaneously stimulating all their structural elements.

8. As the vibratory rhythm of the stream of impulses transmitted by a nerve always corresponds with that of the structures to which its terminal filaments are distributed, any variation of vibratory rhythm transmitted from the cerebro-spinal centers by the general motor nerves gives rise to a corresponding variation of activity in the structures or organs supplied by these terminal filaments.

9. In all the above-mentioned organs the oxidizing substance —a combination of adrenal secretion and oxygen formed in the lungs and of which the blood-plasma is the vehicle—is the physico-chemical agency through which cellular metabolism is sustained during PASSIVE *functional activity, and increased during* ACTIVE *functional activity.*

CHAPTER VII.

THE ADRENAL SYSTEM, THE GENERAL MOTOR SYSTEM, AND THE PNEUMO-GASTRIC NERVE.

THE OXIDIZING SUBSTANCE AND THE DUAL NERVOUS SUPPLY OF THE ORGANS OF DIGESTION.

The oxidizing substance has already shown its ability to subserve the physiological needs of several sets of organs; we will now find it to assume similar functions in the stomach, liver, heart, lungs, etc., notwithstanding the dissimilarity of the functions of these organs. Here, however, the uncomplicated nervous mechanism we have described—all apparently carried on, as far as efferent impulses are concerned, through the agency of the single cerebro-spinal motor system—does not suffice. A new and separate nervous supply seems to demand recognition: *i.e.*, that represented by the pneumogastric nerves.

The Stomach and its Physico-Chemical Functions.—In an able review of the relationship between the nervous system and the production of gastric secretion Howell[1] introduces the following remarks: "It has been very difficult to obtain direct evidence of the existence of extrinsic secretory nerves to the gastric glands. In the hands of most experimenters stimulation of the vagi and of the sympathetics has given negative results, and, on the other hand, section of these nerves does not seem to prevent entirely the formation of the gastric secretion. There are on record, however, a number of observations that point to a direct influence of the central nervous system on the secretion. Thus, Bidder and Schmidt found that in a hungry dog with a gastric fistula the mere sight of food caused a flow of gastric juice, and Richet reports a case of a man in whom the œsophagus was completely occluded and in whom a gastric fistula was established by surgical operation: It was then found that savory foods chewed

[1] Howell: "American Text-book of Physiology," second edition, 1900.

in the mouth produced a marked flow of gastric juice. There would seem to be no clear way of explaining the secretions in these cases except upon the supposition that they were caused by a reflex stimulation of the gastric mucous membrane through the central nervous system."

The Gastric Nervous Supply and the Formation of Gastric Juice.—When the nervous supply of the stomach is closely examined, a rather unusual state of affairs presents itself: *i.e.*, it contains no *bona fide motor* nerves, unless we grant the many sympathetic fibers distributed to it motor qualities, or, refusing to recognize these, accept the vagus as the secretory nerve. But, if we do this, to which nerve must we ascribe the afferent impulses, which the ingestion of various substances that cause nausea and other manifestations which clinicians so often witness induces? The sympathetic has everywhere shown itself as an efferent nerve, and we have already furnished considerable evidence in favor of our view that all sympathetic nerves are but subdivisions of the general motor system. Considered from this standpoint, we could logically account for the phenomena witnessed and relegate to the vagus the rôle of afferent nerve which, judging from its recognized identity as a great sensitive system, normally belongs to it. If, on the other hand, we grant the vagus secretory functions, we have to transform the sympathetic into an afferent nerve, and necessarily controvert all the experimental evidence adduced.

Howell, continuing the remarks quoted above, says: "These cases are strongly supported by some recent experimental work on dogs by Pawlow and Schumowa-Simanowskaja. These observers used dogs in which a gastric fistula had been established, and in which, moreover, the œsophagus had been divided in the neck and the upper and lower cut surfaces brought to the skin and sutured so as to make two fistulous openings. In these animals, therefore, food taken into the mouth and subsequently swallowed escaped to the exterior through the upper œsophageal fistula without entering the stomach. Nevertheless, this 'fictitious meal,' as the authors designate it, brought about a secretion of gastric juice. If in such animals *the two vagi* were cut, the 'fictitious meal' no longer caused a secretion of the gastric juice, and this fact may

be considered as showing that the secretion obtained when the vagi were intact was due to a reflex stimulation of the stomach through these nerves. In later experiments[2] from the same laboratory the secretion caused in this way by the act of eating is designated as a 'psychical secretion,' on the assumption, for which considerable evidence is given, that the reflex must involve psychical factors, such as the sensations accompanying the provocation and gratification of the appetite. In favorable cases the fictitious feeding was continued for as long as five to six hours, with the production of a secretion of about 700 cubic centimeters of pure gastric juice. Finally, these observers were able to show that *direct stimulation of the vagi*[3] under proper conditions causes, after a long latent period (four and a half to ten minutes), a marked secretion of gastric juice. The long latent period is attributed to the simultaneous stimulation of inhibitory fibers." Howell closes his review of this subject by the remark: "Taking these results together, we must believe that the vagi send secretory fibers to the gastric glands, and that these fibers may be stimulated reflexly through the sensory nerves of the mouth, and probably also by psychical states."

That oral sensory nerves and psychical states may reflexly cause increase of secretion of gastric juice we deem demonstrated, not only by experimental physiology, but also by the teachings of clinical experience. As to the nature of the stimuli through which this is caused, the newer conceptions recorded in this work fully sustain the results referred to by Howell when he says, in the foregoing review: "In the hands of most experimenters stimulation of the vagi and of the sympathetics has given negative results, and, on the other hand, section of these nerves does not seem to prevent entirely the formation of the gastric secretion." And, paradoxical as this may seem, there is no ground to doubt the accuracy of Pawlow and Schumowa-Simanowskaja's observation that electrical stimulation of the vagus gave rise to a marked secretion of gastric juice. Still, it seems to us that, had wire been dis-

[2] Pawlow and Schumowa-Simanowskaja: "Die Arbeit der Verdauungsdrüsen," Wiesbaden, 1898.

[3] All italics are our own.

tributed throughout the walls of the stomach and a free end brought out to the exterior and the circuit closed under the same conditions, an equally strong current being used, the results would undoubtedly have been similar. The vagus may have acted as a mere conductor for the transmission of a current which would have simultaneously stimulated all the secretory mechanism: glands, vessels, sympathetic fibers, and muscles.

We know that application of the current to the skin causes contraction of the underlying muscles; can we doubt that the gastric tissue may be similarly affected when so perfectly distributed a conductor as the fibers of the vagus is employed for its transmission? It is evident that a current may serve a useful purpose as it did in Claude Bernard's experiments on the submaxillary or in Laffont's on the mammary gland, *after* vasodilation as a result of division of the nerve had previously shown its physiological purpose; by merely *restoring* the normal state, it afforded confirmatory evidence and a basis for logical deductions. In Pawlow's experiments it is given the leading rôle, however, and, pending further elucidation, it may prove wise to accept as basis of our analysis of the whole subject the following remark of Professor Howell's: "Our knowledge of the means by which the flow of gastric secretion is caused during normal digestion, and of the varying conditions which influence the flow, is as yet quite incomplete," and to build up the process with the aid of what newer factors our own views may suggest.

We may assume, with the quantity of evidence already adduced as groundwork, that the sympathetic fibers are intimately connected with the functional mechanism of the organ. As no true motor nerves have been traced to the stomach, and as we have attributed to the sympathetic system motor functions, may Auerbach's and Meissner's plexuses—both sympathetic structures—not supply all the efferent fibers required by the glands and the muscular coats? Beginning with Auerbach's plexus, we know that after piercing the external serous coat of the stomach its nerves pass between the circular and longitudinal muscular layers, where they form a close network strewn with ganglia, the whole constituting the plexus.

The terminal varicose fibers of this plexus are particularly interesting to us, since they form in the muscular coat of the stomach an *intra*muscular plexus *which entwines*, as it were, *the muscular fibers*. Furthermore, this plexus gives off filaments which, entering deeper into the wall of the stomach, form another plexus, also containing many ganglia: *i.e.*, Meissner's plexus. This net-work of sympathetic elements—fibers, ganglia, cells, etc.—lies in the submucous coat,—*i.e.*, immediately under the muscularis mucosæ, which separates the latter from the secretory glands. Besides the many filaments it distributes to the thin submucous muscular layer, it gives off a large number that penetrate this layer. These, on reaching the glands, form a close net-work in the connective-tissue sheath surrounding them, which net-work gives off delicate fibrils that enter into the glandular elements themselves. They likewise supply terminal fibers to the neighboring muscular elements and to their vascular supply.

The blood-vessels of the stomach are distributed in a very similar manner. Piersol[4] describes them as follows: "The larger arteries, after penetrating the outer coats, divide within the submucosa into smaller branches, one set of which pierces the muscularis mucosæ, to be distributed to the mucous membrane, while the other enters the muscular and serous tunics. The vessels supplying the mucosa form a rich *subepithelial capillary net-work as well as mesh-works surrounding the gastric glands*, the capillaries lying immediately beneath the basement membrane in close proximity to the glandular epithelium. The branches distributed to the outer layers form long-meshed capillary net-works from which the muscle-bundles and fibrous tissue derive their supply." A feature that requires emphasis in this connection is the manner in which the vessels are finally distributed to the mucous membrane: The small arteries or arterioles do not themselves ascend between the glands, but give off fine capillaries that do so. These, by anastomosing with one another, form a very rich plexus which surrounds each glandular tubule in a net-work of close hexagonal meshes. The cellular secreting elements of the glands being covered

[4] Piersol: "Normal Histology," p. 166, 1900.

by a *delicate basement membrane,* the capillaries are thus related to the former precisely as we found them to be in the sweat-glands. Indeed, if the intrinsic structures of the stomach are compared with those of the organs reviewed, it soon becomes evident that the mechanism to which the production of *secretions* is due does not differ from them.

We cannot, however, say the same in respect to the extrinsic vessels and nerves, and to this feature of the process we wish to call especial attention. As is well known, the vascular supply of the stomach is made up of the gastric, pyloric, and right gastro-epiploic branches of the hepatic artery and the left gastro-epiploic and vasa brevia from the splenic. The important feature referred to is this: The gastric, hepatic, and splenic arteries arise from the cœliac axis, and, as shown in the earlier chapters, *the cœliac axis is the first great arterial trunk to receive the blood from the lungs: i.e.,* before the activity of the oxidizing substance in the downward blood-stream has in any way been reduced. Another very suggestive feature is that *the cœliac axis is surrounded by the cœliac plexus, a portion of the solar plexus of the sympathetic,* and that extensions of the cœliac plexus—the gastric, hepatic, pyloric, gastro-duodenal, and gastro-epiploic plexuses—follow the arteries of the same name *to the walls of the stomach.* We thus have, though in a much more imposing form,—one compatible with the importance of the function,—the two structures required by the extrinsic mechanism: arteries with muscular walls and what we have termed "extrinsic constrictor" nerves—since they are sympathetic plexuses—to decrease their lumen and thus increase the rapidity of the blood-stream through the gastric walls, during functional activity.

Another feature requiring our attention is the formation of the gastric secretion. In the blood-plasma we have sodium and potassium chlorides; in the secretion of the stomach these represent the most important and abundant salts, and constitute the source of the hydrochloric acid in the gastric juice, according to prevailing views. Has the oxidizing substance of the plasma any influence upon the formation of this acid? The marked affinity of chlorine for hydrogen seems able to fill the want. It takes it up whether the gas be free or in vulnerable

combinations *extra corpore;* it doubtless does the same in the gastric structures. But here conditions are especially well adapted for such a reaction, if we analyze the question with the aid of thermochemistry. Equal volumes of chlorine and hydrogen can only be kept in an absolutely dark place; diffuse light causes them to slowly unite, while a bright light—sunlight, for instance—brings on such an instantaneous combination of the two elementary bodies that the flask containing them flies into pieces. The fact that this may also be brought on with a magnesium light which, as is the case with sunlight, is rich in chemical rays, indicates that we are dealing with a process in which heat plays a predominant part. Precisely as the sun sends radiations which the earth transforms into heat, so does it, in the experiment mentioned, send radiations which the combined chlorine and hydrogen transform into heat; the mixture absorbs the undulations of the ether and transforms them into *molecular* energy: *i.e.*, heat. But a multitude of familiar every-day phenomena prove that increased molecular energy, or heat, may be procured without light-rays, etc.; the mere rubbing of a match against a dry surface will cause it to light, for instance. That this occurs without in the least involving the need of a chemical body on the substance against which the match is rubbed to start the reaction indicates that friction causes increased vibratory activity in the ingredients of the match-tip, and, these only combining when a given temperature is reached, *heat* must obviously be accepted as the causative factor of the process. Now, a very significant feature in connection with the formation of the gastric hydrochloric acid is the fact that *the combination temperature, when an immediate reaction is obtained between chlorine and hydrogen, is 39.5° C. (103.1° F.), while that of the gastric cavity is about 38° C. (100.4° F.).* The fact that the walls of the stomach, the seat of the blood-flow, must show a higher temperature than this (at least 2 degrees, that of the liver being 106 degrees) pointedly suggests that the formation of hydrochloric acid only occurs when the stomach is brought up to the required temperature.

How this occurs may now easily be surmised: *(1) the extrinsic vascular supply, under the constrictive influence of the*

cœliac-plexus extensions, hastens the speed of the blood-flow through the gastric tissues; (2) the oxidizing plasma, by enhancing metabolism, raises the temperature of the stomach at least the 1.5° C. required to render the formation of hydrochloric acid possible.

The acid is thus formed when needed: a feature quite in accord with experimental data. The parietal cells of the glands, which are the seats of its formation, are only active during digestion, and then increase in size; they continue in this condition as long as the stomach contains food, and then return to their normal size. The following lines of Howell's also tend to indicate that our conception of the process may be the right one: "The chemistry of the production of free HCl also remains undetermined. No free acid occurs in the blood or the lymph, and it follows, therefore, that it is manufactured in the secreting cells. It is quite evident, too, that the source of the acid is the neutral chlorides of the blood; these are in some way decomposed, the chlorine uniting with hydrogen to form HCl, which is turned out upon the free surface of the stomach, while the base remains behind and probably passes back into the blood."

What is the rôle of the pneumogastric in this connection? That it must be possessed of some regulative action upon the circulation is shown by the fact that if, during digestion,—*i.e.*, while the mucous membrane is congested and covered with gastric juice,—the pneumogastric is cut on both sides, pallor of the surfaces at once ensues and the secretion is arrested. If the *central end*—*i.e.*, that toward the brain—be stimulated, the membrane resumes its former color and the secretion is re-established, while stimulation of the stomach end of the nerve produces no effect, according to some observers. Pawlow, however, as previously stated, obtained a marked secretion in this manner—probably by using a stronger current than did his predecessors. We have previously suggested that the latter result might have been due to the fact that the nerve acted as a mere conductor; though an afferent nerve, the vagus must thus have transmitted an *electrical* efferent impulse, while the physiological impulse could not have been transmitted by it. But this objection is removed when we link Pawlow's experi-

ment with the classic one just referred to, inasmuch as in the latter we are dealing with an afferent impulse, *followed by an efferent* impulse. The one experiment, therefore, confirms the other, and we are brought to recognize that the vagus, as regards its gastric functions, can transmit afferent impulses *to* its center *from* the stomach and impulses *from* the center *to* the stomach, the former being evidently sensory and the latter motor. And, indeed, there is considerable testimony to the identity of the vagus as a motor nerve, and, we may add, to the presence of some exceedingly sensitive center in the region mentioned, since marked excitement or emotion—fear, anger, etc.—during digestion will sometimes arrest the latter: *i.e.*, give rise to the effect observed after section of both vagi. As the motor nerves (ex-sympathetic) are efferent nerves, we therefore have two efferent systems connected with the stomach besides the sensory portion of the vagus referred to.

What is the relationship between the vagus and the plexuses overlying the cœliac axis? That the extrinsic vessels are subject to contractile influences similar to those of the organs already described is shown by the fact that, when all nerves distributed to the stomach are cut, the secretion of gastric juice becomes continuous. Relaxation of the vascular supply having been induced, the secretion is doubtless due to the ensuing engorgement of the blood-vessels and correspondingly increased metabolism and temperature: *a repetition of the phenomena witnessed after section of the sympathetic elsewhere.* Again, that the *intrinsic* process in the mucous membrane is also that witnessed in the organs referred to is shown by the following lines by Professor Foster: "When the secretion is very active, the blood flows from the capillaries into the veins in a rapid stream without losing its bright arterial hue. The secretion of gastric juice is, in fact, *accompanied by vascular dilation in the same way as is the secretion of saliva.*" We can, therefore, assume that the cœliac-plexus extensions fulfill precisely the same rôle that the sympathetic branches we have termed "extrinsic vasoconstrictor" did in the other organs, since they belong to the same motor system.

What is the relative function of the two sets of nerves in the gastric structures? To analyze this question a brief

review of the topographical anatomy of the parts is necessary. The following description by Professor Foster not only furnishes anatomical data, but seems to strengthen the general physiological process as we interpret it: "The stomach is supplied with nerve-fibers from the two vagi nerves and from the solar plexus of the splanchnic system. The two vagi, after forming the œsophageal plexus on the œsophagus, are gathered together again as two main trunks which run along the œsophagus—the left in front, the right at the back—to the stomach. The *left,* or anterior, nerve is distributed to the *smaller curvature* and the front surface of the stomach, forming a plexus in which nerve-cells are present; and branches pass on to the liver and probably to the duodenum. The *right,* or posterior, nerve is distributed to the hinder surface of the stomach, but only to the extent of about one-third of its fibers; about *two-thirds of the fibers pass on to the solar plexus.* . . . From the solar plexus, *nerves, arranged largely in plexuses,* pass in company with the divisions of the cœliac artery, coronary artery of the stomach, and branches of the hepatic artery, *to the stomach.* Though the *two* abdominal splanchnic nerves which join the solar plexus (semilunar ganglia) are chiefly composed of medullated fibers, the nerves which pass from the plexus to the stomach are to a large extent composed of non-medullated fibers. All these nerves, both branches of the vagi and those from the solar plexus, lie at first in company with the arteries on the surface of the stomach beneath the peritoneum. From thence *they pass inward, still in company with arteries,* and form, on the one hand, a plexus containing nerve-cells between the longitudinal and circular muscular coats corresponding to what in the intestine we shall have to speak of as the plexus of Auerbach, whence fibers are distributed to the two muscular coats; and, on the other hand, a plexus in the submucous coat, also containing nerve-cells, corresponding to what is known in the intestine as Meissner's plexus. From this latter plexus fibers pass to the mucous membrane; some of these end in the muscularis mucosæ; whether any are connected with the gastric glands, and, if so, how, is not at present known."

Immediately before reviewing these anatomical features

the author had referred to the physiological mechanism leading to the production of the secretion, in the following words: "Seeing that, unlike the case of the salivary secretion, food is brought into the immediate neighborhood of the secreting cells, it is exceedingly probable that a great deal of the secretion is the *result of the working of a local mechanism;* and this view is supported by the fact that when a mechanical stimulus is applied to one spot of the gastric membrane the secretion is limited to the neighborhood of that spot and is not excited in distant parts. This local mechanism may be nervous in nature, or the effect of the stimulus may perhaps be conveyed directly from cell to cell, from the mouth of the gland to its extreme base, without the intervention of any nervous elements; but *the vascular changes at least would seem to imply the presence of a nervous mechanism.*" After the lines previously quoted and referring to those just given, Professor Foster says: "There are no facts which afford satisfactory evidence that any part of this arrangement of nerves supplies such a local nervous mechanism as was suggested above. The importance, however, of such a local mechanism, whatever its nature, and the *subordinate value of any connection between the gastric membrane and the central nervous system,* is further shown by the fact that a secretion of quite normal gastric juice will go on after both vagi, or the nerves from the solar plexus going to the stomach, have been divided, and, indeed, when all the nervous connections of the stomach are so far as possible severed."

We have already emphasized the "subordinate value" referred to by showing that the oxidizing substance was, after all, the functional *principium energeticum,* and that vascular walls, nerves, ganglia, plexuses, etc., were accessories calculated to bring this energizing principle and the cellular elements together. In the cœliac-plexus extensions we have, as previously stated, "extrinsic vasoconstrictors," but, if two-thirds of the right vagus passes to the *solar* plexus, we must have a duplication of motor functions in this location, and, as this same nerve also passes on to the stomach, we have two kinds of nerves distributed over the same structures in much the same manner: an arrangement which extends to the Auer-

bach and Meissner plexuses. The need of such an arrangement at once suggests itself, however, when the influence of stimulus applied to the membrane soon after ingestion of the stimulating agency, as thought by Heidenhain, or some time after, as thought by Pawlow, is recalled.

The sensory filaments of the vagus could alone, from our point of view, produce such results, since we attribute only efferent impulses to the other nerves which all belong to the great motor system. This is sustained by the classical experiment previously referred to, in which stimulation of the *central* end of the cut vagus caused the secretion to reappear—a fact which also demonstrates that the vagus is an autonomous system: *i.e.*, endowed with afferent and efferent nerves. Whether the branches distributed to the solar plexus and the gastric extrinsic vessels are afferent or efferent nerves can now easily be determined. As the functions of the stomach are similar to those of the salivary glands, as previously shown, the increase of secretion caused by stimulation of the stump can only have been caused by conveying *additional* impulses to the normal motor-constrictor impulses and to the rest of the motor functional mechanism: a feature which suggests that *the general motor mechanism (sympathetic) serves to maintain the tonic contraction of the gastric vascular supply and the immanent potentiality of the stomach when it is in the passive state, while the added impulses of the pneumogastric bring on functional activity.* In other words, the great motor system officiates during the *passive* state, while the *vagus system* is superadded during the *active* state.

We can now understand why section of both vagi produces no effect: the motor nerves continue to maintain the tone of the vessels and everything goes on as usual. If these motor nerves are also severed, however, we have general relaxation, as previously explained, and engorgement—secretion. Again, we can better understand the effects of violent emotion upon digestion when it becomes possible to ascribe to a single center or area the effects of the morbid excitement. If the motor system bore the brunt of such influences, these would induce general vascular dilation by lowering functional activity, since the said system sustains general vascular tone: again,

they would give rise, besides, to disturbances in all parts of the organism to which its subdivisions are distributed. Any practitioner is familiar with the fact that a violent emotion immediately after a meal will arrest digestion, followed by its attending phenomena, but give rise to no other symptoms. The vagus center merely fails, under such circumstances, to supply the added energy for the active function, and the food lies in a passive stomach. We have seen that in the experiments of Pawlow and Schumowa-Simanowskaja, referred to by Howell, the "fictitious meal," though it passed out of an artificial opening in the œsophagus, nevertheless caused in dogs a "psychical" secretion of gastric juice. Cutting of the two vagi in these animals, however, prevented its flow: strong evidence in itself that the vagus system is the ruling one during digestion. Finally, and even more to the point, are the experiments of Contejean, referred to by Onuf and Collins in the following words: "Contejean in experimenting upon frogs found that the pneumogastric nerve has a stimulating influence upon the secretion of gastric juice, the sympathetic having but little effect in this direction." Alluding to the results of personal experiments, these investigators further say: "Incidentally we may mention that this conclusion is in harmony with the results obtained by Contejean on the stomach of frogs."

A feature not to be overlooked in this connection is the practical independence of the suprarenal system. Its vast importance in the organism necessarily involves freedom from individual organs. As regards the stomach, we can readily see that the mere constriction of the extrinsic vessels is sufficient to hasten the speed of the blood-flow and the metabolism of the intramural structures.

This does not mean that all fibers of the motor system are passive factors; indeed, it is probable that during peristaltic action the two nerves, by transmitting impulses of varying relative intensity, may underlie the motions observed. The cardiac end of the stomach, for instance, is mainly supplied by motor fibers.

Vomiting is an interesting symptom in this connection. Toxics, we have seen, increase suprarenal activity to a more or

less marked degree, and vomiting is a prominent symptom of acute intoxications. The sudden appearance of a great amount of suprarenal secretion and a corresponding increase of oxidizing substance in the blood would obviously cause not only vomiting, but general gastric activity, were its penetration to the walls of the stomach and the secretory structures not governed in some way. Whether there are both efferent and afferent vagus fibers in the cœliac plexus it is at present impossible to tell; but, even if afferent filaments did not exist, the enhanced activity of the vagus center incident upon the increased local metabolism would act as an efficient controlling factor, since it would assist the motor system—similarly overexcited—in causing enhanced constriction of all the blood-channels. The wealth of nervous structures over the cœliac axis suggests that this protective effect is primarily exerted in this location, thus preserving more or less—according to the power of the toxic—the integrity of the stomach, liver, pancreas, spleen, and other structures supplied through the cœliac trunk.

When all these facts are considered and the kinship of the functions involved with those of organs previously studied is fully appreciated, the following deductions seem warranted:—

1. The nerves of the stomach are derived from two autonomous sources: the general motor system (sympathetic) and the vagus system.

(a) The general motor system supplies efferent nerves, which serve to maintain tonic contraction of the arteries and to insure the functional efficiency of all gastric structures during the passive, or resting, period.

(b) The vagus system supplies both sensory and motor nerves, which excite and govern the functions of the stomach during its active period: i.e., digestion.

2. The extrinsic efferent nerves of the stomach, also derived from the general motor and vagus systems, accompany the organ's arterial supply and jointly constitute its extrinsic vasoconstrictor system: i.e., that through which the blood-flow in the organ is increased.

3. The intrinsic efferent nerves are divided into two sets: (1)

branches of the "general motor system"; (2) branches of the vagus system.

(a) Each branch of the "general motor system" subdivides into two branches: one of these supplies the arterioles; the other subdivides into two branches, one of which is distributed to the muscles and the other to the glands.

(b) The branches of the vagus subdivide in the same manner and inosculate with the general motor filaments and plexuses except with those distributed to arterioles that supply capillaries to the glands, and probably end in the muscularis mucosæ.

4. When the stomach is in the resting state, the general motor nerves alone transmit impulses to all the structures of the organ, including the glands, which during this period elaborate their secretory products.

5. When as a result of physical reflex or psychical stimuli the stomach becomes functionally active, the vagus impulses impose their rhythm upon the general motor nerves, and the vagus system assumes control of the digestive process.

(a) The extrinsic arteries are constricted beyond their normal tonic caliber; the speed of the blood-flow to the stomach-walls is increased and peristaltic action excited.

(b) The intrinsic arteries that do not supply capillaries to the glands are constricted also, thus forcing the blood into these capillaries and inducing glandular activity and the production of gastric juice.

(c) Pepsinogen (?) and rennin are secreted as a direct result of increased metabolism in the central cells.

(d) Hydrochloric acid is secreted as a result of the rise of temperature incident upon increased metabolism, the reaction between Cl and H—when HCl is formed in the parietal cells—only occurring when 39.5° C. (103.1° F.) is reached: i.e., approximately the temperature of the gastric structures during functional activity.

THE INTESTINES AND THEIR PROPHYLACTIC FUNCTIONS.—The stomach is, in reality, but a dilated portion of the general digestive tract. Its four coats—the mucous or glandular, the submucous, the muscular, and the serous—are continued in the intestinal walls, and what variations are present are limited to the mucous and submucous layers and the glandular struct-

ures therein and according to their individual functions. To emphasize the histological similarity between the stomach and intestines referred to, the following description of the arterial and nervous supplies, from the pen of Professor Piersol, is submitted: "The blood-vessels supplying the intestines follow the general arrangement of those of the stomach. The larger vessels pierce the serous and muscular coats, giving off slender twigs to supply the tissues of the tunics; upon reaching the submucosa the vessels form a wide-meshed net-work. Numerous branches then pass through the muscularis mucosæ, to be distributed to the deeper as well as to the more superficial parts of the mucosa; narrow *capillaries* form net-works which *surround the tubular glands,* while beneath the epithelium wider capillaries encircle the mouths of the follicles. From this superficial capillary net-work the veins arise and, passing between the follicles, join the deeper venous plexus, which, in turn, empties into the larger vein of the submucosa. In those parts of the intestine where villi exist special additional arteries pass directly to the bases of the villi, when they expand into capillary net-works, which run beneath the epithelium and around the central lacteal as far as the ends of the villi. These capillaries terminate in venous stems, which descend almost perpendicularly into the mucosa, in their course receiving the superficial capillaries encircling the glandular ducts. Brunner's glands and the solitary and agminated follicles are supplied from the submucosa by vessels which terminate in capillary net-works distributed to the acini of the glands and to the interior of the lymph-follicles." . . . "The nerves distributed to the intestines are arranged almost identically to those of the stomach; they are composed largely of non-medullated fibers, derived from the trunks which pass within the mesentery from the *larger abdominal sympathetic plexuses.* After giving off branches to the serous coat, the nerves pierce the longitudinal muscular tunic to form the rich intramuscular plexus of Auerbach. This is composed of a rich net-work of delicate, pale fibers, at the nodal points of which microscopical ganglia exist; after supplying the longitudinal and outer part of the circular muscular coats the fibers obliquely pierce the latter tunic to gain the submucous tissue, where they form the

plexus of Meissner, which closely resembles Auerbach's nervous net-work within the muscularis, possessing, however, smaller ganglia and somewhat closed meshes. From the plexus of the submucous tunic fibers pass into the mucosa, to form net-works about the glands and to send fibrillæ into the villi."

In analyzing the functions of the intestinal tract it is important to note that two distinct sets of active structures are present: (1) the *secreting* glands of Lieberkühn and of Brunner; (2) the villi of the agminated lymph-follicles (Peyer's patches) and the solitary lymph-follicles.

Secreting Glands.—The glands, or crypts, of Lieberkühn, found in close array throughout the entire length of the intestine, including the colon, are present only in the upper, or mucous, layer. They are simple in construction and recall the sweat-glands, minus the coils and muscle: *i.e.*, a net-work of capillaries and probably nerve-fibrils overlying a delicate basement-membrane which in turn surrounds a single layer of columnar epithelial cells. These cells radiate toward a common center and thus form a minute tube which opens upon the mucous membrane between the villi. Their functional mechanism is doubtless that of all simple tubular glands. As sympathetic fibers are alone found here, we are bound to accept them as motor fibers. Yet only two sets of fibers are necessary: a set to the glandular arterioles deprived of capillaries; another to the secretory cells. During activity the first set (the "extrinsic vasoconstrictors") reduces the caliber of the arterioles, forcing more blood into the capillaries, while the second set incites and governs the activity of the secreting cells.

Howell refers to the crypts of Lieberkühn as follows: "These structures resemble the gastric glands in general appearance, but not in the character of the epithelium. The epithelium lining the crypts is of two varieties: the goblet cells, whose function is to form mucus, and columnar cells with a characteristic striated border. . . . Whether or not the crypts form a definite secretion has been much debated. Physiologists are accustomed to speak of an intestinal juice, 'succus entericus,' as being formed by the glands of Lieberkühn; but practically nothing is known as to the mechanism of the secretion." We have seen that nerve-filaments are distributed to

the secreting cells of the intestines, as stated by Piersol. The functional needs of these structures seem, therefore, to be satisfied. That they secrete mucus seems evident if their histological attributes can be taken as guide. We must express the belief, however, that they have functions other than those theoretically ascribed to them.

Gastric juice does not only fulfill the rôle usually attributed to it during digestion, but it is likewise a powerful antiseptic. Howell refers to this property in the following words: "One of the interesting facts about this secretion is the way in which it withstands putrefaction. It may be kept for a long time, for months even, without becoming putrid and with very little change, if any, in its digestive action or in its total acidity. This fact shows that the juice possesses antiseptic properties, and it is usually supposed that the presence of the free acid accounts for this quality." This might serve as evidence that beyond the pylorus further protection of this sort is unnecessary: evidence of the care with which Nature protects her organic creations. Every structural cell in any way exposed seems to be surrounded not only with prophylactic weapons, but also with second and even third lines of defense to cope with what the first line may have failed to disarm. Removal of the stomach in animals has been followed with return to normal health; it seems plausible that the intestinal tract should also be supplied with means for the protection of its organs.

The material formed in the living crypt of Lieberkühn first presents the form of granules, then becomes transformed into a transparent substance which accumulates in the spaces of the cell-substance. This either constitutes the mucin found in the secretion or represents an antecedent of this material. The secretion proper is clear, viscid, yellowish, and alkaline. That it may possess antiseptic properties is suggested by the fact that a very similar fluid,—*i.e.*, nasal "mucus,"—thanks to the labors of St. Clair Thomson and Hewlett,[5] has been found to prove bactericidal. Paget[6] experimentally ascertained that

[5] St. Clair Thomson and Hewlett: Medico-Chirurgical Transactions, vol. lxxviii.

[6] Paget: Journal of Laryngology, Nov., 1896.

nasal "mucus" killed anthrax bacilli, that Klebs-Loeffler bacilli were almost as actively destroyed by it, and that the virulence of staphylococci and streptococci was reduced. Nasal "mucus," however, is largely made up of serum: a feature which also applies to the secretion of the glands of Lieberkühn.

Brunner's glands, which occur in the duodenum, at the portal of the intestinal canal, would seem to suggest, by their situation and their general conformation, just such a function. While they resemble in general structure the pyloric glands, to which most authors compare them, they also present many characteristics of the mammary lobules, especially in the manner in which their interlobular ducts are disposed. The gland proper is situated beneath the smaller crypts just described,—*i.e.*, in the submucous tissues,—its ducts penetrating to the surface between the villi or into the crypts of Lieberkühn: an indication that there is considerable analogy between their products. Indeed, their secretion is also serous: *i.e.*, blood-plasma relieved of its fibrin, globulins, etc.

The secretion of these two glands is termed "intestinal juice," or "succus entericus," and is regarded by many as capable of acting on starch, proteids, fats, etc., in connection with intestinal digestion: all properties which might not controvert any antiseptic power it might possess through the presence of oxidizing substance and alexins. Professor Foster, however, referring to this supposed action on foods, says: "Even at its best its actions are slow and feeble. Moreover, many observers have obtained negative results; so that the various statements are conflicting." And he adds: "We may, therefore, conclude that at present, at all events, we have no satisfactory reasons for supposing that the actual digestion of food in the intestine is, to any great extent, aided by such a juice."

These two glands are the only ones forming part of the intestinal tissues *per se* to which the protective functions referred to could be ascribed. Hence, the facts that they both produce a secretion so nearly identical to blood-plasma as to be called "serous,"—for the glands of Lieberkühn are the source of serous diarrhœa, and the rice-water discharges of Asiatic cholera, a disease which, as we will show, is the most

acute expression of suprarenal insufficiency,—and that blood-plasma is the normal excipient for chemical protective agencies, suggest the following deduction: *The glands of Lieberkühn and the duodenal glands of Brunner supply a secretion having for its object to asepticize, and prevent the putrefaction of, the intestinal contents.*

A kindred, though far more important, process is the protection afforded the organism where poisons of all kinds are most likely to penetrate the blood-stream: *i.e.*, the organs of the intestinal wall connected with absorption.

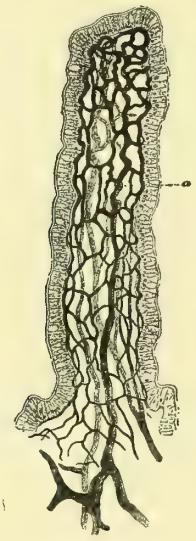
Villi and Lymph-follicles.—The villi, the solitary lymph-follicles, and the agminated lymph-follicles, or Peyer's patches, are considered together, because they appear to us to represent parts of a single system.

The structural similarity between the walls of the stomach and those of the intestine must be set aside here, since the function referred to,—*i.e.*, absorption,—a predominating one in connection with the intestines, can hardly be said to be worth considering as a factor of gastric functions. Conversely, the villi distributed throughout the whole small intestine are especially adapted for this purpose. Besides the capillaries, nerves, muscular tissue, basement membrane, and epithelium, these structures contain a lymph-trunk, or lacteal, the purpose of which is to take up nutritional agencies from the intestinal contents as they pass along.

Each villus may be considered as a sort of "reversed" gland, if a sweat-gland is taken as standard. The epithelium is outside,—*i.e.*, exposed in the intestinal canal,—while under the epithelium lies the basement membrane. Combined, these two constitute a glove-finger-like projection inside of which are the structures that we found *over* the basement membrane in the sweat-gland. The capillaries form a close-meshed network not only in contact with the inside of the basement membrane, but entwined with considerable connective tissue strewn with leucocytes, the tissue and cells constituting "lymphoid tissue." We said "connective tissue," but at this point we must emphasize the fact that it is not *true* connective tissue, as met with elsewhere, but a fenestrated membrane made up entirely of star-like cells that give off thin projections, or

pseudopodia, which by intermixing make up the tissue itself: *i.e.*, Kölliker's *cytogenous tissue*. The fenestra, or openings, with which this cytogenous membrane is permeated accommodate the capillaries.

Another histological feature of special interest is the presence of smooth muscular fibers which stand upright—a few being horizontally disposed—and are interwoven among the capillaries and cell-fibers previously referred to. We thus have immediately under the villus's delicate basement membrane a



INTESTINAL VILLUS; VENOUS RADICLE SHOWN AT *a*. (*Cadiat.*)

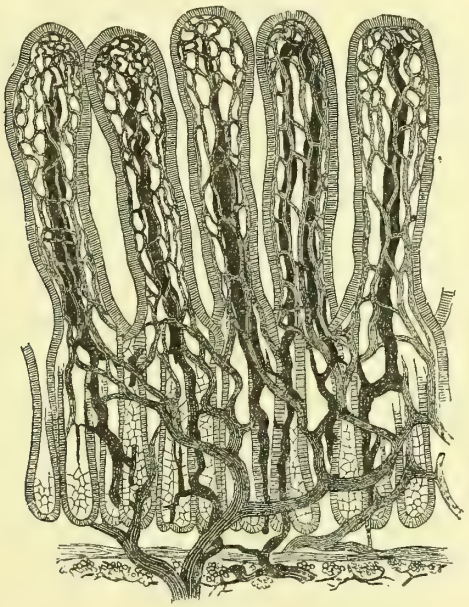
perfect, though minute, suction-pump which by alternately contracting and relaxing causes the organ to absorb the previously asepticized intestinal fluids.

Next in order inwardly are the venous stems (one or two) which carry the blood from the villous capillaries to the veins in the deeper tissues. These vascular channels, which carry the bulk of intestinal foodstuffs to veins which ultimately end in the portal system, are well shown in the annexed cut, and will again be referred to.

Last of all, in the middle of the organ, is the lacteal,—a

thick, club-like, sometimes double, lymphatic vessel, which stands upright and reaches almost to the inside of the tip of the villus, its own blind apex almost touching the former. Each lacteal represents the origin of a lymphatic vessel. This is illustrated in the second figure.

Lymph contains chyle—derived from the intestines—only during intestinal digestion. At other times the fluid found in the lacteal and neighboring structures is identical to that



INTESTINAL VILLI; INJECTED LACTEALS IN THE MIDDLE OF EACH VILLUS. (*Cadiat.*)

found elsewhere in the organism. It is perhaps advisable to emphasize the fact that lymph is very similar to blood-plasma, and richer than this fluid, owing to the presence of leucocytes. Indeed, it only differs from blood in the absence of red corpuscles. It undergoes coagulation and separates, as does plasma, into serum and clot, the latter likewise containing fibrin-globulins. It contains serum-globulin and serum-albumin in relative proportions similar to those in blood, though in smaller quantity: a feature which accounts for its somewhat

lower specific gravity. Inorganic salts, the chlorides preponderating, also correspond to those of the plasma. Being a vehicle for various substances, its constituents are variable quantities, and the conflicting analyses published are thus accounted for. Stewart says, in this connection: "Lymph has been defined as blood without its red corpuscles (Johannes Müller); it is, in fact, a dilute blood-plasma, containing leucocytes, some of which (lymphocytes) are common to lymph and blood, others (coarsely granular basophile cells) are absent from the blood. The reason of this similarity appears when it is recognized that the plasma of lymph is derived from the plasma of blood by a process of physiological filtration (or secretion) through the walls of the capillaries into the lymph-spaces that everywhere occupy the interstices of areolar tissue. But, in addition to the constituents of the plasma, lymph appears to contain certain toxic substances produced in the metabolism of the tissues and destroyed in the lymphatic glands."

It now seems probable that the intestinal tract, being one of the two regions most exposed to toxics, the villi not only have for their function to absorb chyle, but to protect the organism. The lacteal is the recognized absorption organ for emulsified fats. As we view the process involved, the fat-containing fluids, as soon as they reach the basement membrane, are first submitted to the asepticizing influence of its endothelial cells. They are then submitted to the next process of epuration, and probably chemically transformed in the lymphoid layer—Kölliker's cytogenous layer—immediately beneath, in which leucocytes, and, therefore, antitoxic substances, are *constantly being formed.* When it finally reaches the lacteal, it again meets endothelial walls, and when through these and in the lacteal, must run the gauntlet of an accumulated array of fresh leucocytes from the cytogenous layer. The chyle, therefore, is met as soon as it enters the organism by all the latter's protective resources: phagocytes, stellate or connective-tissue cells, endothelial cells, and finally the oxidizing substance, the latter probably serving here to convert products of local metabolism and other toxic materials into inert bodies.

The villi, which thus absorb all nutrient substances assimilated by the organism whether by their venous stems or

their lacteals, are thickly distributed throughout the entire length of the small intestine. In the duodenum and jejunum they doubtless fully satisfy the needs of the organism, both as to absorption and prophylaxis. In the lower part of the intestinal canal, however, more protection is required, owing perhaps to continued exposure of the contents to a relatively high temperature during the time elapsed since this material has been submitted to powerful antiseptic treatment in the stomach: *i.e.*, several hours to a day, according to the meal. A morning movement of the bowels, for instance, includes products of the breakfast of the preceding day, thus representing twenty-four hours of exposure in the intestine to a temperature averaging 39° C. (102.2° F.). This additional precaution is represented by the solitary lymph-follicles and the agminated lymph-follicles, or Peyer's patches. While the solitary lymph-follicles are found throughout the entire canal, small and large, they are by far most numerous in the lower part of the ileum and in the first part of the colon. Peyer's patches, or the agminated follicles, are likewise found in the duodenum and jejunum, though rarely in the former; but their site of predilection is also in the ileum, and, inasmuch as they vary from one-half inch to four inches in length and are oval or round, they cover an extensive area, though only twenty to thirty in number. Especially is this the case since they are practically limited to one side of the intestine: *i.e.*, to the portion facing the latter's attachment to the mesentery. They also frequently form a continuous layer in the vermiform appendix.

A single "solitary follicle" is typical of them all, including those in Peyer's patches. A follicle consists, on the whole, of a rounded mass lodged in the submucous tissue, a small part of its upper portion appearing upon the free surface of the latter, though the epithelium of the intestine also covers it. The overlying layer of epithelium, however, is separated from the follicle by a special delicate membrane perforated with a multitude of holes that surround its projecting portion and communicate with the organ itself.

The structure of the body of the follicle will perhaps be best understood if it is divided into three different parts, be-

ginning from the inner portion of the organ. A fine net-work of capillary blood-vessels which acts as a supporting fabric, furnished by underlying arterioles, is the central feature; this, in turn, is surrounded with a close net-work of fibrils, in which "lymph-corpuscles, small round cells, with a large nucleus and very little perinuclear protoplasm" so completely preponderate as to almost entirely obscure the net-work.[7] But there is a feature of special interest here which will remind us of the cell-forming membrane of Kölliker found in villi: *i.e.*, a central nodule, described by Flemming, in which some cells undergo active karyokinetic division, while others, lymphocytes, are formed in continuous quantities. "In the center of the nodule," say Böhm and von Davidoff,[8] "the cells often show numerous mitoses, and it is here that an active proliferation of the cells takes place. The cells may either remain in the lymph-follicle or the newly-formed cells are pushed to the periphery of the nodule and are then swept into the circulation by the slow lymph-current which circulates between the wide meshes of the reticular connective tissue." The third portion is the interval referred to, a delicately partitioned sinus which surrounds the follicle. To this sinus the lymph, originally from the blood-capillaries, after it has permeated the meshes and cell-spaces of the adenoid tissue and became charged with the newly created cells, gravitates, to finally find its way into the lymph-vessels of the submucous tissues beneath.

The physiological functions of the follicle seem plain when we consider two salient features of its anatomical relations with the mucous surface of the intestine and with the villi. As to the relationship between the interior of the follicle and the intestinal canal, it is suggested by the perforations to which we have previously referred, but there seems to be no mechanism to insure absorption. The case is not the same, however, in respect to the connection with the villi. Indeed, the lymphatic vessels which originate from the lacteals of the latter *constitute the afferent supply of the sinus*, while the lymphatic vessels of the submucous tissue represent its efferent system.

[7] Clarkson: "Histology," 1896.
[8] Böhm and von Davidoff: *Loc. cit.*

It is very evident, therefore, that we have, in each follicle, a powerful adjunct to the overlying villi, to add still another prophylactic means to those already enumerated. While the villi do not occur upon the portion of the follicle that projects into the intestinal free surface, they are nevertheless present *around* it, and their lacteals when below the level of the epithelium break up into vessels which find their way to the lymph-sinus. "When they reach the level of the closed follicles," says Berdal,[9] "the chyliferous vessels become united to the sinuses of these follicles, of which they constitute the afferent vessels. Crossing the muscularis mucosæ, they form part of a varicose capillary net-work in the submucosa. From this net-work arise true lymphatic trunks supplied with valves that cross the intestinal coats and then reach the subperitoneal lymphatic net-work."

The intimate relationship between the villus and the lymphatic follicle is further emphasized by the similarity which their mechanisms present. If the lymph-sinus of the latter is considered as functionally encircling what in the villus has been termed *cytogenous tissue* by Kölliker, including its net-work of capillaries, this similarity becomes striking. Indeed, the fact that the sinus is situated around the lymphoid tissue instead of in its center, as it is in the villus, would tend to indicate that the follicle does not absorb intestinal fluids, since these would merely, before reaching the sinus, be subjected to what epuration the epithelium and the fenestrated membrane overlying the organ could afford. It is, therefore, probable that the solitary follicle or organ does not include absorption among its attributes. Indeed, unless possessed of a suction mechanism such as that of the villi, it is evident that, surrounded, as is its projecting part, by these minute pumps, its usefulness would be very slight.

What can be the use, therefore, of the minute apertures encircling the projecting part of the follicle and which constitute the "fenestrated" subepithelial membrane? "These orifices appear," says Berdal, "to afford passage to lymphatic cells that emigrate from the follicle toward the cavity of the

[9] Berdal: "Histologie Normale," p. 365, 1894.

intestine,"—and to assist, if considered from our standpoint, *in asepticizing the contents of the lower end of the small intestine by permeating it with mobile phagocytes and alexocytes.* If we now connect this fact with the predilection of Peyer's patches for bacterial invasion in typhoid fever, it would seem as if functional impairment of these organs would render possible the pullulation of pathogenic organisms in the ileum. This would normally lead to infection of the patches, and of the system at large through the apertures.

Besides this first, and we may add, very important protective function, the follicular sinus, by serving as a secondary passage for the chyle, appears to afford a supplemental protection to the organism of no mean power when we consider that it serves not only as a channel for freshly-manufactured leucocytes, but that the follicle simultaneously receives freshly-oxidized blood directly from the great arterial trunks, through the mesenteric arteries. This blood, which reaches the lymphoid tissue through the rich intrinsic capillary net-work to which we have referred, doubtless furnishes it with the various elements required for the metamorphoses—retrogressive and progressive—noted by Flemming and others, then forces its way into the sinus, carrying with it not only the newly-created cells, but also serum supplied with all the defensive agencies which the blood affords. The accumulation of Peyer's patches in the lower two-thirds of the ileum seems to directly point to this as the most toxic part of the canal—and clinicians well know how frequently this region becomes the seat of intestinal disease.

It would thus appear as if in the duodenum, the jejunum, and the upper part of the ileum, the gastric juice, the secretion of the crypts of Lieberkühn and that of the glands of Brunner, in addition to the ultravillous process, would subserve the protective process; and that beyond this, to the end of the ileum, the follicles, either solitary or agminated in patches, the villous process *plus* the folliculous process, including the output of lymphocytes into the intestine, united to accomplish the same prophylactic purpose.

Solitary follicles are also very numerous in the cæcum; while in the vermiform appendix agminated follicles they are

sometimes so plentiful as to have suggested to some anatomists the presence of a great Peyer patch. If the production of lymphocytes through the upper fenestrated layer is a function of the follicles here as it is in the ileum, the appendix would have, as its physiological function, the production of quantities of leucocytes intended to prevent the pullulation of bacteria in the cæcum: a region which, owing to its conformation, must lend itself admirably to the accumulation of putrefactive matter. The colon is deprived of villi, but plentifully supplied with crypts of Lieberkühn, while solitary glands, somewhat larger than those in the ileum, are scattered throughout its entire extent. The former doubtless furnish the mucus, while the latter probably contribute the asepticizing lymphocytes.

These views, as far as they go, are sustained by experimental data. We must state, however, that the sympathetic system alone—our general motor system—does not account for other phenomena to be studied elsewhere in this work. While the tabular plan on the next page, illustrating the nervous mechanism down to the adrenals, explains all effects ascribable to efferent impulses, *afferent* impulses are as necessary here as they are in the stomach to initiate the secretions of the glandular structures and, if need be, augment them. The presence of vagal filaments can, therefore, be assumed pending the presentation of confirmatory testimony.

After stating that "the influence of special nerves upon the secretion of intestinal juice has not been studied as yet," Onuf and Collins refer as follows to the disturbances that result from extirpation of the stellate ganglion in cats: "They consisted of diarrhœa and putrefaction of the fæces. The fæcal matter was semiconsistent, of yellow or dark-grayish-brown color, and of exceedingly foul odor. This putrefaction of the fæces was observed in two of the three animals from which we removed the stellate ganglion. In the third cat they were not noted; but it should be added that this cat was killed before a time corresponding to that which had elapsed antecedent to the occurrence of putrefaction in the first two cats. The putrefactive symptoms made their appearance as late as two or three months after the operation, and it was noted that the digestive disturbances had a tendency to in-

crease and persisted until the death of the animals, three and four and one-half months, respectively, after the operation. In one instance the autopsy revealed marked anæmia of the intestines."

ORGANS OF THE DIGESTIVE TRACT SUPPLIED BY THE SOLAR PLEXUS.

(*a*) *Phrenic plexus*
- Diaphragm.
- Suprarenal glands.
- Through its diaphragmatic ganglion
  - The inferior vena cava.
  - Suprarenal capsules.
  - Liver.

(*b*) *Suprarenal plexus.* (Also includes subdivisions of the solar plexus, semilunar ganglion, phrenic, and great splanchnic. Branches of this plexus are remarkable for their large size.) — Suprarenal glands.

(*c*) *Cœliac plexus*
- Cœliac axis.
- Stomach.
- Liver.
- Spleen.
- Pancreas.
- Duodenum.
- Epiploön.

(*d*) *Superior mesenteric*
- Mesentery.
- Pancreas.
- Small intestine.
- Part of colon.

(*e*) *Aortic plexus*
- Mesentery.
- Part of colon.
- Sigmoid flexure.
- Rectum.

We are dealing, in these experiments, less with the effects of section of intestinal nervous supply on the local vascular walls than with those of impaired suprarenal functions, the connection between the adrenals and the anterior pituitary on one side being removed. Decrease in the suprarenal substance supplied to the blood, and therefore of oxidizing substance in the plasma, was the main morbid factor. The functional energy of the intestinal crypts, glands, and follicles being im-

paired through loss of part of their *pabulum energeticum* in the blood, the asepticizing secretion of the crypts of Lieberkühn and the glands of Brunner became reduced, the production of lymphocytes by the follicles likewise, while the reduction of oxidizing substance in the secretions *per se* contributed to further impair their prophylactic qualities. Onuf and Collins also refer to one of their animals operated in the same way, in which diarrhœa developed in two weeks; the third week "the animal began to be uncertain in gait, which increased to well-marked staggering" . . . "within two days it died in collapse." That these phenomena are of suprarenal origin needs hardly to be emphasized.

The following deductions seem to us to be warranted by the analysis submitted:—

The glands of Lieberkühn and the duodenal glands of Brunner supply a secretion the purpose of which is to asepticize the intestinal contents.

The villi, through their venules and lacteals, absorb nutrient and chyle-forming materials from the intestinal foodstuffs, and the contents of the lacteals are submitted to a further asepticizing process, mainly in Kölliker's cytogenic membrane.

The solitary and agminated lymph-follicles (Peyer's patches) are cytogenic structures which further asepticize the materials absorbed by the surrounding villi, the efferent lymph-vessels of the latter constituting the afferent lymph-vessels of the follicles, where both kinds of organs occur together: i.e., in the portion of the small intestine in which pullulation of pathogenic bacteria is most likely to occur, the ileum particularly.

The solitary and agminated lymph-follicles also supply leucocytes to the intestinal cavity, which leucocytes are formed in their cytogenic area (Flemming's central nodule) and pass out through the fenestrated membrane overlying each follicle. The purpose of some of these leucocytes is to insure the destruction of pathogenic bacteria formed as a result of putrefaction of the intestinal contents or introduced into the intestine.

The cœcum, being particularly exposed to the accumulation of putrefactive materials, is supplied with an organ in which agminated lymph-follicles are particularly numerous: i.e., the vermiform appendix. The functions of this organ, therefore, appear to be to

supply the cæcum with bactericidal cells and their products: i.e., phagocytic leucocytes and alexocytes—in addition to those supplied by the cæcal agminated follicles—and antitoxic blood-serum.

In the colon, the asepticizing process is fulfilled by a rich supply (1) of Lieberkühn's crypts, which keep its walls bathed with their muco-serous secretions; and (2) of irregularly scattered solitary lymph-follicles, which supply the latter secretion with bactericidal cells and their alexins.

The nervous supply of the intestines is derived from the general motor system (ex-sympathetic nerves) and from the vagal system, the distribution to the various intestinal coats being similar to that of the branches of the same system in the stomach. The vagal system probably alone excites and regulates intestinal functions during digestion as well as during intervals.

The Liver and its Physico-Chemical Functions.—There is considerable evidence available to show that oxidation is one of the most active factors of hepatic functions, and yet it must be admitted that, according to prevailing views, there is no blood-supply capable of accounting for this powerful source of energy. To the portal vein, essentially a channel for physiologically impotent blood,—*i.e.*, blood replete with the waste-products of four important organs and the oxygen of which has been utilized in these organs,—is ascribed this preponderating rôle. On the other hand, the hepatic artery is thought to supply the liver "with the blood of nutrition." Text-books on physiology, therefore, seldom refer to this vessel; works on histology hardly grant it more than two or three lines, if they refer to it at all. In text-books on anatomy it receives more attention, but only in its general topographical bearing.

As viewed from our standpoint, *the hepatic artery does not only supply the liver with its nutritional blood, but simultaneously with the blood upon which all its functions depend.*

To develop this proposition a review of the histology of the lobule is necessary. Clarkson[10] gives the following complete, though succinct, description of this wonderful little body

[10] Clarkson: "Text-book of Histology," 1896.

—about one-twentieth of an inch in diameter—and which in itself has been termed a "miniature liver":—

"A lobule of the liver is polygonal in shape, and is composed chiefly of a number of gland-tubes, which radiate from near the center of the lobule to the periphery, where they open into their ducts. Thus, the blind terminal end of the tube is turned toward the center of the lobule; the ducts at the periphery lie in the interlobular connective tissue, which to the naked eye marks the boundaries of the lobule.

"The blood brought to the liver by the *portal vein*[11] is conveyed along its subdividing branches till the ultimate subdivisions are reached, which lie, together with the bile, in the connective tissue surrounding the lobules. Here capillaries are given off which pierce the lobule and pass between the radiating gland-tubes to reach the center, where they open into the intralobular radicle of the efferent vein of the liver, the *hepatic vein.* These small hepatic radicles open into the larger vessel, —the *sublobular vein,*—and the sublobular veins unite to contribute to the hepatic vein itself. The walls of the branches of the hepatic vein are destitute of muscular fibers and the adventitia is extremely thin. The radiating gland-tubes anastomose laterally with each other, as do the capillaries also. The meshes of the net-works are elongated in a radial direction. Thus, a lobule is composed of a radiating system of gland-tubes and a corresponding radiating system of capillaries lying between them. A very minute quantity of connective tissue accompanies the capillaries as an adventitia and in this lymphatic channels are to be found separating the gland-tubule from the blood-vessel.

"The lobule is surrounded (in part or whole) with connective tissue supporting branches of the afferent portal vein, —the feeder of the capillary net-work,—and the *bile-ducts,* which receive the secretion of the gland-tubules. Thus, the blood flows from the periphery to the center of the lobule; the bile, from the center to the periphery.

"But in addition to the afferent portal vein and the bile-ducts another vessel is found in the interlobular connective

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[11] The italics are our own.

tissue. This is the *hepatic artery,* which supplies blood for the nutrition of the connective tissue of the organ, the vessel-walls, etc. It ultimately terminates in the small portal veins, and perhaps partly in the capillaries in the periphery of the lobules."

There exists some uncertainty as to the manner in which the subdivisions of the hepatic artery are related to the other perilobular and intralobular vessels. Pick and Howden[12] refer to its terminal distribution as follows: "Finally, it gives off interlobular branches, which form a plexus on the outer side of each lobule, to supply its wall and the accompanying bile-ducts. From this lobular branches *enter the lobule* and end in the capillary net-work between the cells. Some anatomists, however, doubt whether it transmits any blood directly to the capillary net-work." Harrison Allen[13] says: "Each lobule is a miniature liver having at its periphery between the lobules branches of the portal vein and hepatic artery (interlobular branches) which freely *intercommunicate* and form *through the lobule,* between its periphery and center, a capillary net-work. Directly at the center the venules of this net-work (intralobular vessels) converge to form radicles of the hepatic vein." Labadie-Lagrave[14] states that, "as regards the divisions (of the hepatic artery) destined for the lobules, they penetrate conjointly with interlobular veins, *but without communicating* with them, in the interior of the lobule, in the form of capillaries distributed to the *central vein.*" In the presence of these divergent views, which but exemplify those of other authors, our only choice lies in the selection of the one region which all authors seem to consider as reached by the artery: *i.e.,* the periphery of the lobule. But, as all concede, also, that the arterial capillaries penetrate in one way or another to the intralobular supply, we will adopt—though we believe that Harrison Allen's definition is the true one—the more conservative distribution indicated in the annexed engraving by Piersol, who, in accord with many histologists, describes the

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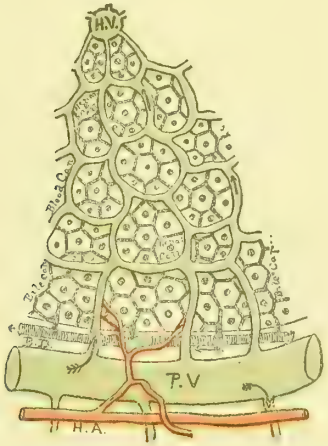
[12] Pick and Howden: "Gray's Anatomy"; edition, 1901.
[13] Harrison Allen: "Human Anatomy," 1884.
[14] Labadie-Lagrave: "Traité des Maladies du Foie," 1892.

hepatic artery as "supplying nutrition to the interlobular structures and terminating in the lobular capillary net-work."

A noteworthy feature of the capillary net-work enveloping the cellular bodies is that each mesh does not merely cover one cell, but several. Indeed, were it otherwise, the bile-capillaries could not exist as individual channels and give an uninterrupted free way to their contents without allowing the bile to penetrate the blood-stream. To prevent this, and yet simultaneously insure perfect exposure to the blood and lymph, a very simple arrangement exists: *i.e.*, three or more of the



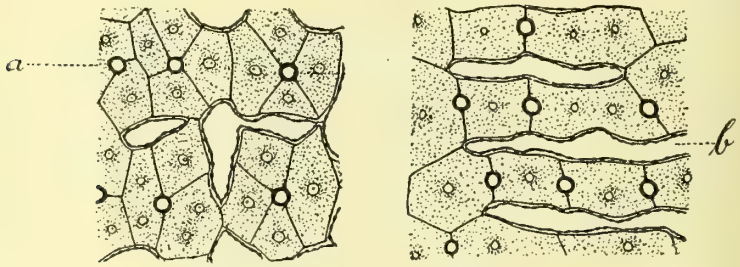
SECTION OF LIVER SHOWING THE LOBULES, CELLS, AND THE BLOOD-SUPPLY. (*Piersol.*)

P.V., Portal vein. H.A., Hepatic artery. H.V., Hepatic vein.

cells (usually polyhedral) are joined longitudinally, and, while the narrow passage in the center of the group thus formed serves as a bile-channel, the outside only is in contact with the blood- and lymph- capillaries. When only two cells are thus joined, the surfaces in contact have in their center a small opening, which, being adjusted to that of the adjoining cell, insures the continuity of the channel. It thus becomes clear that the blood-plasma may penetrate the cell, undergo or induce metabolism therein, and the product pass out through the intercellular biliary passages or bile-capillaries. The cells

are so joined as to form continuous, though correlated, channels, which radiate from the center of the lobule to its periphery, where they join the interlobular bile-channels.

The intimate structure of the hepatic cell is peculiar. It possesses no limiting membrane; but its peripheral protoplasm is more dense than that of its other parts and the pseudocovering so formed serves as the outer wall for numerous cavities or vacuoles which inosculate irregularly throughout its interior. All these vacuoles, however, more or less directly converge toward the center, where they meet a protoplasmic mass, which in turn contains one and sometimes two nuclei. The cell, apart from its nucleus, suggests a miniature sponge the cavities of which (secretion vacuoles) become filled with



BILIARY CANALICULI. (*Mathias Duval.*)

a, A biliary canaliculus cut transversely. *b*, Intercellular capillary.

glycogen. This substance seems to accumulate in the *outer* vacuoles, which appear wider in this location than the inner ones, when, by artificial means, the glycogen has been removed. It is perhaps noteworthy that this substance accumulates in the part of the cell nearest the blood-vessels and that the droplets, or "granules," considered as bile are most abundant in the opposite direction: *i.e.*, near the bile-capillaries. These "droplets" accumulate between periods of digestion and diminish during this process. A delicate canaliculus connects this part of the cell with the biliary channel. The vacuoles in the paraplasm, according to Kupffer, "play an important part in the secretion of the cell, and are due to the confluence of minute drops of bile into a large globule. As soon as the vacuole has attained a certain size it tends to empty its con-

tents into the bile-capillary through a small tubule connecting the vacuole with the bile-capillary." Kupffer's main vacuole is thought by him to constitute an intracellular vesicle connected with the bile-capillaries by means of delicate tubes.

The nerves of the liver enter the organ at the transverse fissure and accompany the blood-vessels and lymph-vessels to the interlobular spaces. That the sympathetic and the pneumogastric supply these nerves and that "minute ganglia occur along the interlobular trunk" represent about all the information to be gleaned from classical books. Berkley traced several divisions of the intrinsic nerves; "no doubt, the neuraxes of sympathetic neurons," observe Böhm and von Davidoff, who add: "The suggestion seems warranted that these terminal fibrils are the endings of sensory nerves. Some of the nerve-fibers following the bile-ducts may be traced into the hepatic lobules. The intralobular plexus is formed, therefore, by the terminal branches of the non-medullated nerve accompanying the portal and hepatic vessels and the bile-ducts." Pflüger has contributed interesting complemental evidence, however, which confirms the existence of the pericellular nervous network that we have observed in all other glandular structures; indeed, he not only noted the presence of a plexus around the cell, but also ascertained that terminal filaments perforated its protoplasmic peripheral thickening. On the other hand, Nestorowski and Kolatschewski found a terminal plexus around the intralobular capillaries, while Miura, who confirmed the latter observation, also ascertained that this vascular plexus could be traced to the intralobular vessels (Labadie-Lagrave[15]). This establishes a connection with the extrinsic nerves, down to the transverse fissure referred to at the beginning of this paragraph, and indicates that the liver is innervated, as we found the stomach and pancreas to be, by vagal and sympathetic extensions from the cœliac plexus.

Our inquiry into the character and composition of the substances that are transformed in the liver and of the secretions of this organ must necessarily include the blood of the portal vein, since it contains whatever products of metabolism

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[15] Labadie-Lagrave: *Loc. cit.*

the organ is thought to transform. We shall, therefore, begin with this channel, which brings to the liver essentially venous blood, since it contains that utilized by four organs—the stomach and the intestines, the pancreas and the spleen—in which the metabolic products include, besides those incident upon ordinary tissue-waste, food metabolites, physiological toxics, etc.

As is well known, there exist in the liver's secretions distinct evidences of association with splenic hæmatopoietic or hæmolytic functions. The liver is known to modify the composition of the blood as it passes through it, but the purposes of the alterations involved are not established.

The path from the spleen to the portal vein, through the splenic vein, is a direct one, and the blood the spleen sends to the liver is not, therefore, submitted to modifications in transit by any other organ, though the splenic *vein* receives a few branches from the pancreas and stomach. Still, these are mere tributaries to a common channel, and, as the arterial supply comes directly from the cœliac plexus, we can say that the spleen receives nothing but pure, freshly-oxygenated blood in great quantities. Indeed, the splenic artery is remarkably large for the dimensions of the organ, and *we can easily account for the so-called "ague-cake" and the temporary enlargement that occurs during malarial and other fevers when we include suprarenal overactivity in the pathogenesis of these phenomena.*

To this we cannot ascribe, however, the post-prandial splenic enlargement, which attains its maximum about five hours after an ordinary meal, since we now know how independently of suprarenal overactivity and merely through nervous influence an organ's function can be excited and governed; indeed, sympathetic and pneumogastric again unite here to account for a *passive* period and for an *active* period: that of gradual enlargement. "The turgescence of the spleen seems to be due to a relaxation both of the arteries and of the muscular tissue of the capsule and of the trabeculæ" says Professor Foster: evidence that we are again dealing with vasoconstriction of some arterioles to shift the blood-stream into the functional areas,—a repetition of what we have found to exist in other organs. Obviously the constriction and shift-

ing does not, as we have previously said, require an increase of the *quantity* of blood distributed to an organ. A striking confirmation of this fact occurs in the following lines of Professor Foster's: "The pathway of the blood through the splenic reticulum is peculiar; and increase or decrease in the volume of the spleen means more or less blood held in the spleen-pulp, not necessarily a greater or less flow of blood through the organ."

That the organ is concerned with some process incident upon blood-changes is evident. But what is this process? The various points that may afford a clue are these: red blood-corpuscles have been found in various stages of disorganization in the organ, but in the interior of amœboid cells buried in the pulp. The spleen-pulp also contains an albuminoid proteid rich in iron, and a pigment which shows considerable carbon. That an active combustion process may go on in the organ is suggested not only by the latter, but also by the presence of various purin bases: xanthin, hypoxanthin, and their end-product, uric acid. Various other acids—acetic, butyric, formic, succinic, lactic, etc.—are also found in relatively large quantities. This appears suggestive when we consider—if our views are sound—the large quantity of oxidizing substance that must course through the organ especially during post-prandial activity.

The spleen also seems to be a leucocytogenic center, since the splenic vein contains a much larger proportion of leucocytes than the splenic artery. But as these leucocytes leave the organ through the splenic vein, and ultimately, therefore, reach the liver through the portal, they must either be connected with some function in the liver or be destroyed there. Again, the arterial blood has been found to lose one-half of its red corpuscles; at least, blood from the spleen contains one-half of those found in the blood of the splenic arteries. Coupled with the finding of disorganized remnants of these bodies in the splenic pulp, this certainly suggests, as is generally believed, that red blood-disks are disintegrated and white corpuscles created in the spleen. Indeed, the portal blood is poor in red disks. Yet, the hepatic vein is still poorer in them in the sense that the proportion of red to white cells is as

four in the subhepatic vein is to one in the portal vein, after the blood has been submitted to the effects of hepatic functions. It seems clear, therefore, that red corpuscles are destroyed both in the spleen and in the liver, and that, since the spleen is possessed of no external duct, it is in the liver's secretions that we should find proofs of this dissociation of corpuscular elements. Indeed, we have in bilirubin, a bile-pigment derived from hæmoglobin, direct evidence of this fact.

The Hepatic Blood-pigments. — We have already analyzed (in the second chapter) the process through which various blood-pigments are transformed one into another. We will now only refer, therefore, to the features which suggest the purposes of the spleno-hepatic functions as regards these bodies.

We ascertained that the changes undergone in the liver represented but a portion of a cycle of which the intestines were the starting-point, bilirubin (excepting that transformed into urobilin and stercorin) being reabsorbed from the intestine and again used in the building up of hæmoglobin. Experimental evidence was adduced to show (Macallum) that in an animal fed on albuminate of iron free leucocytes crowded with iron-pigment could be traced in transit through the intestinal mucous membrane in the villi, and that similar leucocytes had been found in the spleen and in the liver. But can we conclude from this that the iron-laden leucocytes find their way to the spleen and that this organ constitutes a part of the cycle? The anatomical relations of the structures involved show that, even if such an arrangement did exist, it could serve no useful purpose, since the leucocytes would but penetrate the splenic structures to again enter the portal circulation. Obviously, the only pathway available anatomically is the venous one, since Macallum found the "leucocytes crowded with granules of iron-pigments" in the *venules* of the villi.

The single venous channel at our disposal, therefore, is that of the distribution of the villi, the ileum and jejunum mainly, *i.e.*, the superior mesenteric veins,—which again lead us to the portal vein. This probably means that the iron thus taken from the intestine is not ready for the circulation, and

that it must undergo a secondary process in the liver before it can serve its physiological purpose in the arterial circulation. This is sustained by the prevailing view as to the functions of the spleen, *i.e.*, that it disintegrates worn-out red corpuscles, and also by the great increase of leucocytes observed in the splenic vein as compared to the proportion of these cells in the artery. It therefore seems logical to conclude that *both in the lymphatic structures of the intestine and in those of the spleen leucocytes are formed which carry iron-pigments to the portal vein; those from the intestine reach the latter by the superior mesenteric vein, and those from the spleen by the splenic vein.* As Macallum observed iron-pigment leucocytes in the spleen similar to those witnessed in the intestinal villi, and the venules of the latter and the splenic vein ultimately transmitting their blood to the portal vein, no other conclusion seems possible.

The similarity of the general mechanism involved suggests the presence of correlated functions. Thus, *in the spleen the leucocytes are formed in situ, pass out into the pulp-channels, and take up the iron-pigment and carry it out to the liver; in the intestine they are formed in a similar structure,—the follicle,—pass out into the intestinal channel, take on a similar supply of blood-pigment, re-enter through the villi into the venous system, and also proceed to the liver.* True, we have previously ascribed bactericidal properties to the leucocytes produced by the intestinal follicles; but the chemotactic property of the leucocytes, the existence of which is shown by their ability to take up the pigments, serves but to demonstrate that they must also be endowed at least with phagocytic attributes.

We also ascertained, in the chapter referred to, that, while the adrenals supply an oxidizable substance to the blood, insufficiency of the adrenals leads to the formation of a compound inferior to hæmoglobin in oxygen-absorbing powers,—*i.e.*, methæmoglobin; and, furthermore, that hæmatoporphyrin is formed when the suprarenal insufficiency is still further advanced, hæmoglobin being unable to hold itself together, as it were, and to absorb oxygen. Again, we saw that hæmoglobin is reduced to hæmatin when the reaction with the reducing agent occurs in the *presence* of oxygen. In the *absence* of oxygen

a hæmochromogen is formed which slowly loses its iron, the end-product being also hæmatoporphyrin.

It is evident that the integrity of the hæmoglobin molecule is dependent upon the quantity of secretion that the adrenals supply to the blood, and also upon the condition of that molecule at a given time. In other words, while the adrenals may be supplying their normal proportion of secretion, the hæmoglobin molecule in the red corpuscles of venous blood—*i.e.*, blood about to return to the vena cava for a fresh supply—may be compared to that of blood during insufficiency. Even as hæmoglobin, the blood-pigment is loosely combined; when approaching the end of its systemic circle, it is still nearer the state of disintegration—according to the activity of the oxidation processes which it has subserved. Starting from the lungs as oxyhæmoglobin, it may return to the heart as hæmoglobin or reduced hæmoglobin, ready to at once absorb another supply of suprarenal secretion and, once in the lungs, take up its oxygen.

Blood from the head, extremities, and other structures in which the drain upon its resources has not been excessive, returns such a molecule to the heart; it is still efficient as an oxygen-carrier. *But not so with the blood from any organ directly connected with the digestive system.* As is well known, all the blood from the organs of the alimentary tract—stomach, intestine, pancreas, and spleen—is not returned to the heart before it has been submitted to whatever action the liver may have upon it; then only can it re-enter the circulation through the hepatic veins, which carry the blood to the vena cava. But not all the blood may thus be rejuvenated; some has gone beyond; it has, indeed, almost reached the state of hæmatoporphyrin, the last on the list of pigments, that which appears in the most advanced stages of suprarenal insufficiency. We have seen that hæmatoporphyrin and bilirubin are similar; and, as is well known, it is bilirubin which passes out with the bile.

A salient feature of the hæmoglobin molecule is missing here, however, namely: the iron. As stated, a reducing agent, if used in the presence of oxygen, will reduce hæmoglobin in the absence of oxygen; the primary product is a hæmochromogen which gradually parts with its iron, leaving as end-

product hæmatoporphyrin. As bilirubin and hæmatoporphyrin are fundamentally identical, the presence of the former in the bile must be the result of a similar process in the liver. That such is the case is sustained by considerable collateral evidence, first of which is the invulnerability of the hæmoglobin molecule.

Paradoxical as this statement appears, it nevertheless constitutes the key-stone of the entire edifice, since it is only when *vulnerable* that the molecule becomes the prey of disintegrating influences. We have used the words "reducing agents" several times; but the hæmoglobin molecule does not yield to even moderately-strong reagents of this nature; indeed, only a powerful agent—sulphuric acid, for instance—will dissociate it: an exemplification of the wonderful binding power which the suprarenal secretion must exert upon all its constituent parts. Still, we must not overlook the fact that the oxidizing substance in the blood-plasma is identical to this binding compound. Indeed, we have accumulated so much testimony affirming the fact that the plasma *per se* is a potent source of energy, while the red corpuscles always played so secondary a rôle in the various intrinsic functional mechanisms, especially those concerned with muscular and glandular elements, that we have been led to conclude that the red disks are, after all, but servants of the blood-plasma: pack-mules, as it were, from which it can draw, as needed, enough oxidizing substance to maintain its own functional potentiality as previously stated.

Under these circumstances we can readily see how the hæmoglobin molecule, gradually deprived of its binding oxidizing substance during the inordinate metabolism which the tissues of the digestive organs undergo during their periods of activity, should yield more readily to dissociating influences. It is evident that a molecule so weakened, thrust in blood such as that of the portal vein,—a vast sewer replete with physiological waste-products and deoxidized blood-cells, all bathing in a plasma itself despoiled of its oxidizing substance,—should soon become dissociated. Transported through gradually narrowing channels, the walls of which, like all tissues, eagerly absorb any loose oxygen that it may contain, it must inevitably undergo the transformation of hæmoglobin referred

to, *i.e.*, into the primary hæmochromogen, which soon drops its iron, leaving as end-product bilirubin.

We have here the identical process that occurs in the brain or other structures when blood-clots are disorganized into hæmatoïdin preparatory to absorption. "The bile-pigments originate from hæmoglobin" says Professor Howell; "this origin was first indicated by the fact that in old blood-clots or in extravasations there was found a crystalline product, the so-called 'hæmatoïdin,' which was undoubtedly derived from hæmoglobin, and which, upon more careful examination, was proved to be identical with bilirubin. This origin, which has since been made probable by other reactions, is now universally adopted." That the influence of the suprarenal secretion rests upon as solid a foundation is illustrated by the experiments of Boinet, who found the blood of a large number of rats from which he had removed the adrenals replete with "hæmatoïdin."

To trace the itinerary of the two products, iron and bilirubin, through the liver, naturally brings the hepatic cell within the scope of our inquiry, since we have to account for the transfer of the former to the bile and the return of the iron to the general circulation.

The functional importance of iron in the hæmoglobin molecule is generally recognized. Yet, the pigments, when separated from it, are not unable to take up oxygen. Indeed, we have ample evidence of this in the formulæ of the very products of which bilirubin is the primary compound. Thus, while bilirubin is $C_{16}H_{18}N_2O_3$, biliverdin is $C_{16}H_{18}N_2O_4$, and the latter can readily be prepared artificially from the former by oxidation. "It is supposed that, when the blood-corpuscles go to pieces in the circulation," says Howell, "the hæmoglobin is brought to the liver, and then, under the influence of the liver-cells, is converted into an iron-free compound: bilirubin or biliverdin. It is very significant to find that the iron separated by this means from the hæmoglobin is, for the most part, retained in the liver, a *small portion* only being secreted in the bile. It seems probable that the iron held back in the liver is again used in some way *to make new hæmoglobin* in the hæmatopoietic organs." We have seen that *it is not under the influence of the liver-cells, as now believed, that hæmoglobin is dis-*

sociated: an important feature, since it removes the main element of confusion from our path. Indeed, we can now easily account for the retention of the greater part of bilirubin in the liver, since we have at our disposal all the constituents for the synthetic production *within* the portal capillaries of the hepatic lobule of new hæmoglobin, and particularly oxidizing substance, brought there by the terminals of the hepatic artery.

On examining, on page 329, the illustration from Piersol's work, the distribution of the hepatic artery's terminal arterioles or capillaries will be found to be unusual. Immediately above the margin of the lobule—*i.e.*, where the portal or interlobular vein breaks up into the capillary net-work of the lobule—the hepatic arteriole may be seen to open *into* the portal capillary. The inference is obvious. *The hepatic artery coming directly from the cœliac axis, brings freshly oxidized blood,—i.e., oxidizing substance,—which, mixing freely in the narrow channels of the lobule with the portal blood, at once groups bilirubin and iron, and builds up all the hæmoglobin that the constituents present (including what iron the splenic leucocytes and those from the intestinal follicles have brought) allow. What bilirubin cannot, owing to deficiency of either of the other constituents, be utilized, becomes an excretory product; and with many others it enters the hepatic* CELL *and is passed out with the bile.*

That deficiency of suprarenal-oxidizing substance can increase the excretion of bilirubin has been repeatedly shown herein. We may refer, for example, to the many forms of acute poisoning and to the diseases attended with suprarenal insufficiency in which there is increased excretion, either in the urine or fæces, of hæmatoporphyrin, methæmoglobin, urobilin, stercobilin, etc.: *i.e.*, of some derivative of hæmoglobin.

We have referred to the hepatic cell as a miniature sponge. This comparison, due to Berdal, is especially warranted, since Schäfer[16] noted the existence, within this cell, of canaliculi which are in direct communication with the blood-capillaries. Having injected carmine gelatin into the portal vein, the colored substance filled this vessel and its subdivisions, besides the canaliculi, but no other structure. It may, therefore, be

[16] Schäfer: Journal of Physiology, Jan. 31, 1902.

inferred, says Professor Schäfer, "that the injection has passed directly from the blood-vessels into the liver-cells; indeed, here and there one can see what appear to be such direct communications." These can readily be seen in the annexed illustration. He refers to the conclusion reached by Browicz,[17] based on appearances, normal and pathological, "that there must exist a net-work of nutritive *canals* within the hepatic cells which are in direct communication with lobular capillaries"; this he had not as yet, however, verified by injections. Schäfer's observation probably accounts for the direct transfer of the bilirubin to the biliary capillaries, along with other

LIVER OF RABBIT INJECTED FROM THE PORTAL VEIN. THE INJECTION HAS PASSED INTO CANALICULI WITHIN THE LIVER-CELLS. (*E. A. Schäfer.*)

products of oxidation, to which we will refer later on. Indeed, J. W. and E. H. Fraser[18] are also stated to have found intracellular *passages* communicating with the blood-vessels in the hepatic cells of frogs. For the present it seems logical to conclude that one or more of the canaliculi may lead to the vacuole previously referred to as nearest the bile-capillaries, and that it is in this vacuole that bilirubin joins the bile. That even this vacuole is supplied with a canaliculus we have already

[17] Browicz: Bulletin de l'Académie des Sciences de Cracovie, 1899.

[18] J. W. and E. H. Fraser: Journal of Anatomy and Physiology, vol. xxix, p. 240, 1895.

seen; Kupffer found it to afford a direct channel between this bile-reservoir and the bile-capillaries *per se.*

The Hepatic Tissues in their Relations to Bacteria.—A prominent feature of the work so far done is the evidence furnished that several physiological processes now ascribed to the hepatic cell in no way involve this structure, and that the portal vein itself and the *intercellular*[19] capillaries are the seat of several of these processes.

Before proceeding further, however, reference must be made to the connection between bacteria and the *normal* liver. We emphasize "normal" here, because we thus simultaneously lay stress upon a feature which plays a predominating rôle in disease: *i.e.,* the fact that anatomically, as far as bacteria go, there is no direct normal connection between the digestive system and this organ. The liver, in fact, is essentially a physiological organ in the sense that it is mainly intended to rid the system of waste-products and to economize others that may again prove useful, by preparing them for reabsorption in the intestine.

We have seen that the venules of the villi allow iron-pigment leucocytes to enter the mesenteric veins which carry their blood to the portal. A depraved condition of all the digestive structures—such as that induced by alcoholism, for instance—can so lower the functional activity of these structures as to cause these venules to lose their normal turgescence and afford passage to bacteria, alcohol in large doses being known to impair metabolism. The intestinal venules under these circumstances, surrounded by weakened protective structures, can well give passage to Adami's cirrhosis bacillus, for instance, or any other capable of coping with what prophylactic conditions may still prevail. "The portal vein can transport to the liver morbid germs from the intestinal surface," says Labadie-Lagrave. "One of the best established pathogenic connections of this kind is the influence exerted upon the development of hepatitis by dysentery; although this relationship is not constant, all observers have noted it. Phlebitis

[19] We find it necessary to give the terminals of the portal this name in order to avoid confusion; they contain blood from both the portal and hepatic channels, and in reality form part of both as extensions.—S.

starting from an ulcerated area and directed toward an hepatic focus has also been observed. When the primary portal structures are normal, transmission of the putrid material may occur through the lymphatics. While this fact seems admissible, it has not been verified." Again, pathological conditions of the stomach, pancreas, or spleen may supply the portal vein with pathogenic elements. In the normal subject, however, *the liver-tissues per se are totally isolated anatomically from any of the structures that come into contact with exogenous bacteria*, precisely as they are in other organs: the muscles, the heart, etc. That its blood-stream affords protection from disease is undoubted, however, judging from the leucocytes that are constantly entering the organ, and the perivascular lymphatic channels. That the portal vein is also an important field for the splitting of toxalbumins and their reduction to harmless bodies we shall also see. But it seems quite clear that the liver itself is not primarily a germ-killing organ, and that its attributes are essentially chemical. This removes the hepatic cell still further from the functions now attributed to it, and suggests that the oxidizing substance in the lobular blood-vessels may be the main source of the liver's functional activity.

This brings us to the consideration of the functions in which the oxidizing substance in the blood-plasma acts as a reagent. We have already reviewed, in this connection, the synthesis of hæmoglobin; we will now take up and consider two equally important subjects: *i.e.*, the origin of urea and the conversion of sugar into glycogen.

Urea and its Formation.—We will first analyze an experiment by Schröder[20] in which the liver was taken from a freshly-killed dog and irrigated through its blood-vessels by a supply of blood taken from another animal. Howell refers to this experiment in the following words: "If the supply of blood was taken from a fasting animal, then circulating it through the isolated liver was not accompanied by any increase in the amount of urea contained in it. If, on the contrary, the blood was obtained from a well-fed dog, the amount of urea con-

[20] Schröder: Archiv für exper. Pathol. und Pharm., Bd. xv and xix, 1882 and 1885.

tained in it was distinctly increased by passing it through the liver, thus indicating that the blood of an animal after digestion contains something that the liver can convert to urea."

Considered from our standpoint this experiment has another meaning. During digestion, especially after copious feeding, as stated above, the entire organism is, to a certain degree, involved in the digestive process, as shown by the general sense of heat often experienced under these conditions. As liver, intestines, pancreas, and spleen, even after gastric digestion has passed, are all operating together, the suprarenal activity is doubtless enhanced. In other words, at such times the blood contains either in its corpuscles or in its serum a more or less marked increase of oxidizing substance. Conversely, the fasting dog's blood—especially if the fasting has been prolonged—is really abnormal blood, in which the oxidizing substance is unusually low, since suprarenal activity is depressed with that of the rest of the tissues. We have also seen that, under these conditions, the tissues nevertheless continue to absorb their normal supply of oxygen, the blood being thus actively depleted while insufficiently oxygenated. It seems clear, therefore, that the blood of the well-fed dog contained more oxidizing substance than that of the fasting one.

That the injected blood taken from the well-fed animal should have been the source of the urea-forming substance is unlikely. Since the liver alone receives alimentary waste-products, it is only with blood from the portal vein that such substances could have been obtained. This is not specified. The urea-forming agent must, therefore, have been in the excised liver's portal channels, and the only available agency capable of inducing the reactions involved appears to be the oxidizing substance. Experimental evidence may be adduced to show that such is the case. We consider the blood of the hepatic artery, as previously stated, as the source of supply of the oxidizing substance, since it is directly derived from the cœliac axis. Stewart states that, "although the portal vein carries a much greater supply of blood than the hepatic artery, *ligation of the latter* causes a greater diminution in the ratio of the amount of urea to the total nitrogen in the urine than

ligation of the former. This seems to indicate that oxidation plays an important part in the formation of urea in the liver (Doyon and Dufourt)."

That the substances thus oxidized reach the liver by the portal vein needs hardly to be emphasized. But Foster says: "The introduction of even a small quantity of proteid material into the alimentary canal at once increases the urea in the urine, and in the curve of the discharge of urea in the twenty-four hours each meal is followed by a conspicuous rise. . . . We have seen reason to think that the proteids of a meal are absorbed not by the lacteals, but by the portal blood-vessels, and such bodies as leucin probably take the same course. This being so, all these bodies pass through the liver and are subjected to such influences as may be exerted by the hepatic cells."

Such bodies of leucin—one of the main products of nitrogenous dissociation—naturally follow the same course. Drechsel has suggested that all bodies of this class—*i.e.*, leucin, tyrosin, glycocoll, etc.—first undergo oxidation in the tissues, and that their ammonia and carbonic acid then combine synthetically, forming ammonium carbamate, this, in turn, being carried to the liver and there transformed into urea.

It is clear that these ammonia compounds take the course outlined by Foster: *i.e.*, the venules of the villi, the mesenteric veins, and finally the portal vein. That they undergo oxidation in the blood of these vessels, however, is not likely, for they contain probably the most watery blood of the organism, and that most depleted of its oxygen.

Quite another field of activity is afforded, however, when the hepatic lobule is reached; *here the ammonia compounds meet the oxidizing substance brought by the hepatic artery's capillaries.* Taking the ammonium compound referred to by Drechsel for example, the series of reactions outlined by him seem to follow in normal sequence: 1. In the portal vein: hydrolytic cleavage with the formation of amido-bodies, such as leucin, tyrosin, aspartic acid, glycocoll, etc. 2. In the hepatic-lobule capillaries and their oxidizing substance: oxidation, with the formation of ammonia, carbonic acid, and water, followed by the synthetic union of ammonia and carbonic acid,

forming the carbamate of ammonium. This being dehydrated, urea is formed, as shown in the following equation:—

$$CO<^{NH_2}_{ONH_4} - H_2O = CO<^{NH_2}_{NH_2}$$

That the conversion of ammonia compounds into urea does occur in the liver is sustained by experimental physiology. Howell refers to the experiments of Schröder, in which this is demonstrated as follows: "As further proof of the urea-forming power of the liver, Schröder found that if ammonium carbonate was added to the blood circulating through the liver —to that from the fasting as well as from the well-nourished animal—a very decided increase in the urea always followed. It follows, from the last experiment, that the liver-cells are able to convert carbonate of ammonium into urea. The reactions may be expressed by the equation:—

$$(NH_4)_2CO_3 - 2H_2O = CON_2H_4."$$

The foregoing facts, considered collectively, indicate that the formation of urea in the liver is probably accomplished in the following manner, taking Drechsel's series of reactions as standard of the numerous ones of the same class that must occur in this organ:—

Granting that the *nitrogenous* bodies are absorbed by the venules of the intestinal villi and transmitted by the mesenteric veins to the portal vein, the ramifications of which would then carry them to the hepatic lobules, *the first reaction would occur in the prelobular portal vessels: i.e., the nitrogenous bodies would undergo hydrolysis, with the formation of amides, leucin, aspartic acid, tyrosin, etc.* The second reaction would follow as soon as these bodies reached the pericellular capillaries, owing to the presence therein of the oxidizing substance supplied by the terminal branches of the hepatic artery; in other words, *further reduction of these bodies by oxidation to ammonia, carbonic acid, and water would occur in the pericellular capillaries of the lobule.* The third reaction would seem, like the first, to require comparatively inert surroundings: *i.e.*, a fluid not charged with oxidizing substance as is the blood of the pericellular capillaries. Such a medium we have, in all likelihood,

in the afferent venous channels, since it is very improbable that any oxidizing substance, so precious in all physiological functions (at least so it appears to us), should be wasted in vessels ultimately ending, *via* the hepatic veins, in the inferior vena cava. Hence, whether it involved a preliminary formation of an ammonic carbamate or proceed to immediate synthesis, *it appears as if the terminal reaction ending in the formation of urea occurred in the efferent venous hepatic channels.*

The salient point of this series of reactions is the fact that, contrary to the general belief, they *all occur, not in the hepatic cells, but in the blood-stream of the lobular capillaries.* The following facts show this to be the case: It is clear that, if urea is formed in transit through the vessels of the organ, it should appear as soon as, or at least soon after, its causative agencies are introduced in the portal system. We will recall the quotation from Professor Foster's text, in which he says: "The introduction of even a small quantity of proteid material into the alimentary canal at once increases the urea in the urine, and in the curve of the discharge of urea in the twenty-four hours each meal is followed by a conspicuous rise, etc." When we consider that the entire circulatory circuit occupies but twenty-six seconds, the cause of the rapid appearance of urea—heretofore unexplained—becomes apparent.

When the rôle of the oxidizing substance in the production of uric acid from the alloxuric bases was analyzed in the third chapter, uric acid was considered as the end-product of a series of reactions in which, according to modern views, these toxic nuclein derivatives were converted into benign ones. All nitrogenous products being transferred to the portal system, it now seems clear that normally the reaction must occur in the intercellular capillaries of the hepatic lobules, and that it is when this oxidation process in the liver is inadequate that the so-called "uric-acid diathesis" symptoms occur. As uric acid leaves the organism, as does urea, by the urine, it is evident that we are again dealing with a function totally disconnected from the hepatic cell *per se.* Again, we have repeatedly seen, in the preceding chapters, that the elimination of phosphoric acid was increased by the administration of suprarenal, pituitary, and other organic extracts and by various

drugs. As will be seen later on, the increased excretion due to drugs always coincides with suprarenal overactivity, hence with enhanced oxidation. It thus becomes apparent that *many constituents of the urine, normal and abnormal, the origin of which is obscure, are due to variations in the oxidation processes in the intercellular capillaries of the liver, caused by corresponding fluctuations in the functional activity of the adrenals.*

Glycogen and its Formation.—Glycogen obviously removes our inquiry from the arteriole to the hepatic cell, since this organ is that in which it accumulates; but we must not lose sight of the important fact that two processes are involved in the analysis,—(1) the formation of the glycogen and (2) its conversion into dextrose,—and that the latter reactions must occur in the vascular channels. Again, the first process seems so bound up with the formation of the bile that it becomes necessary to consider this subject simultaneously to avoid repetition.

The sponge-like construction of the hepatic cell due to its vacuoles, the delicate canals described by J. W. and E. H. Fraser, Browicz, and Schäfer, and finally, the bile-collecting vacuole, or vesicle, leading through its own canaliculi to the perilobular bile-capillaries, does not appear to afford much room for protoplasm capable of undergoing functional metabolism, since this would have to be embodied in the partitions separating all these cavities. Yet, were it otherwise, the nucleus—often duplicated, particularly in herbivorous animals, almost one-third in size that of the entire cell, and containing nucleoli—would represent a useless structure. It seems evident, judging by the appearance of the cell as a whole, therefore, that the nucleus, which, as we have seen, is surrounded by a thin limiting layer of protoplasm, must impart its energy to this layer. This, in turn, being the central terminal of all the partitions, which, along with the cell's own pseudocovering, are protoplasmic, the vacuoles become receptacles, as it were, of the products of their walls.

Again, when we behold the minute canals so clearly shown in Schäfer's illustration (shown on page 340) a direct communication with parts external to the cell is evident in several places, and it seems clear that, if his carmine gelatin could

penetrate through these, so could an equally viscid substance, and with still greater ease, the blood-plasma. As "no injection in the intercellular bile-canaliculi nor in the perivascular lymphatics nor between the cells" could be detected, the penetration of the gelatin can hardly be ascribed to undue stress. "There being," also, "no diffusion of carmine nor any staining of the cells or nuclei by carmine," the nucleo-mural net-work to which we refer must be an independent structure, circumscribing two kinds of cavities: the canals and the vacuoles. The canals communicating with the exterior of the cell, they are probably the receiving cavities, while the vacuoles, their neighbors, are the spaces in which the *useful* products of metabolism are accumulated. The canals themselves, continuing until Kupffer's vesicle is reached, would thus pour their excretory contents—bile and its various constituents—into this cavity, and this, in turn, would convey them to the intercellular bile-capillaries through its own canals.

Whether so direct a connection between the intercellular capillaries and the bile-channels through the cell exists is a point to be determined. Bile and the various bodies excreted with it would be voided as are the intestinal contents, the canalicular walls taking up certain elements, while physiological substances would be mixed with the substances in transit for definite purposes.

The first question that suggests itself is the following: Is glycogen formed during the *active* functional activity of the liver (during digestion) or during its *passive* state (between meals)? We have seen that the production of urea is increased immediately after a meal; we have evidence, therefore, that an active state based upon increased oxidation processes must prevail, and that it is during digestion that the substances out of which glycogen is formed reach the liver, *i.e.*, while the oxidizing substance is present in the capillaries. This suggests that the oxidizing substance must itself take part in the formation of glycogen, though perhaps *indirectly*, and also in the elaboration of bile.

The main coloring constituent of bile, bilirubin, we have previously considered as the product of a reaction in the intercellular capillaries. As such it is probably eliminated with the

bile merely because its high oxygen constituent places it beyond the limits of further oxidation. Yet we have in another component of bile, biliverdin, evidence that some oxidizing process occurs during the passage of bilirubin through the cell, under certain circumstances,—perhaps when more oxidizing substance is present,—for Howell says: "Biliverdin is supposed to stand to bilirubin in the relation of an oxidation product. Bilirubin is given the formula, $C_{16}H_{18}N_2O_3$, and biliverdin, $C_{16}H_{18}N_2O_4$, the latter being prepared readily from pure specimens of the former by oxidation."

With this evidence that oxidation does play some rôle of the processes involved, it will facilitate our task to briefly review the mutual relations of main biliary constituents. By far the larger proportion of these is made up of the bile acids, namely: the sodium salts of cholic acid,—*i.e.*, glycocholic and taurocholic acid. These are obtained from cholic acid *derived itself from sugars and fats* (Voit). Now, Tappeiner[21] found that cholic acid yielded fatty acids *on oxidation*, and, since taurocholic and glycocholic acids are fatty acids, this suggests that they become such during their passage through the hepatic cells and as the result of an oxidation process.

The various phases of the process in the hepatic cells become clear when the oxidizing substance is included as one of the intrinsic factors involved. The blood-plasma of the portal vein contributes the sugars and fats (along with the waste-products to be excreted), while the hepatic artery supplies plasma containing the oxidizing substance. All three active agents meeting in the canaliculi, a part of the sugar (according to the proportion of oxidizing substance present) and all the fat (if the proportion of oxidizing substance is not abnormally reduced by suprarenal insufficiency) are oxidized into cholic acid. But, as the blood also contains glycocoll (probably collagen-cartilage, mucin, connective tissue, and gelatin-waste), glycocholic acid is formed. Again, since the blood likewise contains taurin (probably muscle and pulmonary-tissue waste), taurocholic acid is formed. Just the amount of oxidizing substance necessary being supplied by the hepatic

[21] Tappeiner: Zeitschrift für Biologie, Bd. xii, S. 60, 1876.

artery to each lobule, to properly regulate the functions involved, only the required sugar is burnt by the oxidizing substance. The rest, under the influence of the nuclei of the hepatic cells and the mural protoplasm of the latter, is converted into glycogen and collected in the adjoining alveoli.

But we must also account for the elimination of the many waste-products that are found in bile. An interesting feature connected with these fatty acids is that they can combine synthetically with other bodies, even with proteids, while they are simultaneously able to emulsify the more insoluble soaps and other fatty acids and thus insure their elimination. Again, cholesterin, mainly derived from the white matter of the cerebro-spinal axis and nerves (Flint), in which it occurs in abundance (Foster), was formerly considered as a fatty substance capable of undergoing saponification, but it is now classed among alcohols: the only alcohol that occurs in the organism in a free state. This body is not only soluble in solutions of the biliary acids also, but it *combines* with acids, including glycocholic acid. The importance of this fact appears when it is recalled that insufficiency of glycocholic acid in this connection—and also, perhaps, of oxidizing substance—is the main source of gall-stones. The cholesterin being a constant constituent of bile, when there is not enough glycocholic acid present to take it up, it is precipitated in the gall-bladder and there forms the calculi of which it is the main component. Another body derived from nervous structures, but which, like cholesterin, is to be found in other fluids, especially blood-serum, is lecithin. This body, besides others not mentioned, only occurs, however, in very limited proportions.

It is now evident that glycocholic acid and taurocholic acid should be looked upon as *functional* acids, in the sense that they are not only vehicles for waste-products of metabolism, but are also capable of submitting them to dissociating reactions under the influence of the oxidizing substance. They are sources of energy precisely as myosinogen appears to be a source of energy, and capable of becoming factors of combustion phenomena when in contact with the latter substance. They are also truly physiological in the sense that they serve to recover or economize those products which can again be

used by the organism. Indeed, they (or at least a part of their decomposition products) are again absorbed by the intestinal mucous membrane, and, passing through the venous channels, probably take up therein and transfer to the hepatic cells what waste-matter they are to carry to the intestinal tract. We thus have in the cellular canaliculi two acids endowed with powerful affinities and an active reagent, the oxidizing substance, to account for the processes of a chemical nature connected with the functions of the hepatic cell.

Of course, all this involves the necessity of showing, as a controlling factor, that products of combustion are also present. The following lines by Professor Howell give this feature due emphasis; referring to bile, he says: "The secretion contains also a *considerable, though variable, quantity of* CO_2 *gas*, held in such loose combination that it can be extracted with a gas-pump without the addition of acid. The presence of this constituent serves as an indication of the extensive metabolic changes occurring in the liver-cells."

Again, the element of nervous control implied when we referred to the oxidizing substance contributed by the hepatic artery must be shown. We have seen that the vagus was the *active* nerve during functional activity of the stomach; that it should likewise govern hepatic functions is obvious. That such is the case is sustained by no less an authority than Claude Bernard, to whom we owe the discovery of glycogen—one of his greatest achievements—and whose conceptions have been almost all sustained by all the labor bestowed upon them since. He not only found that the vagus was the predominating nerve in the liver, but that its section also suppressed its glycogenic function.

The fate of glycogen, its conversion into sugar for the use of muscular and other tissues, may now be analyzed with greater facility.

Our analysis of muscular functions led us to the deduction that the contractile elements contained a substance, myosinogen, which, when brought into contact with the oxidizing substance of the plasma, became the source of the muscle's working energy. Ample evidence was afforded to show that we were dealing with an oxidation process, the intensity of which

was commensurate with the amount of blood that the arterioles supplied to the contractile tubular elements. There seems to be considerable analogy between this process and that which prevails in the hepatic lobule. Howell alludes to this in the following words, which well recall the fact that we referred to glycogen as the main constituent of myosinogen: "The history of glycogen is not complete without some reference to its occurrence in the muscles. Glycogen is, in fact, found in various places in the body, and is widely distributed throughout the animal kingdom. It occurs, for example, in leucocytes, in the placenta, in the rapidly-growing tissues of the embryo, and in considerable abundance in the oyster and other mollusks. But in our bodies and in those of the mammals generally the most significant occurrence of glycogen, outside the liver, is in the voluntary muscles, of which glycogen forms a normal constituent."

The similarity between muscular and hepatic sources of energy is further emphasized when, in the following paragraph, Howell says: "In accordance with the view given above of the general value of glycogen—namely: that it is a temporary reserve-supply of carbohydrate material that may be *rapidly converted into sugar and oxidized*,[22] *with the liberation of energy* —it is found that the supply of glycogen is greatly affected by conditions calling for increased metabolism in the body. Muscular exercise will quickly exhaust the supply of muscle and liver glycogen provided it is not renewed by new food. In a starving animal glycogen will finally disappear, except perhaps in traces; but this disappearance will occur much sooner if the animal is made to use its muscles at the same time. It has been shown also by Morat and Dufourt that, if a muscle has been made to contract vigorously, it will take up much more sugar from an artificial supply of blood sent through it than a similar muscle which has been resting; on the other hand, it has been found that, if the nerve of one leg is cut so as to paralyze the muscles of that side of the body, the amount of glycogen will increase rapidly in these muscles as compared

[22] The italics are our own.

with those of the other leg, that have been contracting meantime and using up their glycogen."

These facts clearly indicate that oxidation processes are not in order here, since glycogen is a source of energy, intended, therefore, for subsequent oxidation wherever it is distributed. Indeed, Professor Foster remarks, in this connection: "It was formerly believed that this sugar underwent an immediate and direct oxidation as it was circulating in the blood. . . . It is sufficient for us at the present to admit that the sugar is made use of in some way or other." Referring to the physiological uses of glycogen, he also says: "The main purpose of the deposition of glycogen is to afford a store, either general or local, of carbohydrate material, which can be packed away without much trouble so long as it remains glycogen, but which can be drawn upon as a source of soluble circulating sugar whenever the needs of this or that tissue demand it." That the oxidizing substance has nothing to do with the process is clear.

The conversion of glycogen into sugar in the liver appears as a wasted function, the carbohydrates having been already split into dextrose or dextrose and levulose in the portal system. Why they do not merely pass on to the several tissues seems strange. But it soon becomes evident that, were it otherwise, sugar would accumulate, then be excreted by the kidneys, and lost, since there can only be a fixed and limited (0.1 or 0.2 per cent.) amount of sugar in the circulation at a given time. So useful a substance is, therefore, stored, after dehydration, in the hepatic cell as glycogen, and converted into sugar according to the needs of the organism.

Conversion of the liver glycogen into dextrose is generally ascribed to a special ferment, thought to originate in the liver, but the nature of which has remained undetermined. The experiment of Claude Bernard, upon which this view is mainly based, is the following, as related by Stewart: "A rabbit, after a large carbohydrate meal—of carrots, for instance—is killed and its liver rapidly excised, cut into small pieces, and thrown into acidulated boiling water. After being boiled for a few minutes the pieces of liver are rubbed up in a mortar and again boiled in the same water. The opalescent aqueous extract is

filtered off from the coagulated proteids. No sugar, or only traces of it, is found in the extract, but another carbohydrate —glycogen, an isomer of starch, giving a port-wine color with iodine and capable of ready conversion into sugar by amylolytic ferments—is present in large amount. Again, the liver, after the death of the animal, is left for a time *in situ*, or, if excised, is kept at a temperature of 30° to 40° C. or for a longer period at a lower temperature; it is then treated exactly as before, but no glycogen, or comparatively little, can now be obtained from it, although sugar (dextrose) is abundant. The inference plainly is that after death the hepatic glycogen is converted into dextrose by some influence which is restrained or destroyed by boiling. This influence may be due to *an unformed ferment* or to the *direct action of the liver-cells*, for both unformed ferments and living tissue-elements are destroyed at the temperature of boiling water."

Another explanation suggests itself to us if, instead of a ferment of hepatic origin, we hypothetically use one of external origin: In the first procedure immediate immersion in boiling water destroyed the ferment which happened to be in the blood-vessels, while, in the second, the ferment was given time to act. The difference in the conclusions vouchsafed is simply this: no thought being given to the blood-vessels, the ferment could only be considered as of cellular origin. We have seen how many functions ascribed to the hepatic cells really belonged to the intercellular blood-stream; this seems to be an additional one.

Admitting that we are dealing with a ferment of external origin, from which organ could we expect it to be derived? Can we attribute the process to ferments from the salivary glands or pancreas? If it is produced only by digestive ferments,—*i.e.*, amylolytic ferments poured out during digestion, —why does glycosuria appear irrespective of any digestive process when the floor of the fourth ventricle is punctured, as shown by Claude Bernard? He also found that conversion of glycogen into sugar was a continuous process, carried on to subserve the needs of the organism: a perfectly logical conclusion if the liver is really a storehouse for this substance. Again, the quantity of sugar in the blood, as we have seen,

is small, but constant. How could we account for these features of the problem with ferments transmitted through the digestive tract?

Finally, sugars thus produced—*i.e.*, from amylolytic ferments secreted by the digestive tract—do not seem to be dextrose, the sugar produced by the supposed hepatic ferment. Thus, Professor Foster says: "In the case of the amylolytic ferment of saliva, pancreatic juice, intestinal juice, and, indeed, of all other amylolytic animal fluids, the sugar into which starch or glycogen is converted is *maltose*. Now, the sugar which appears in the liver after death is dextrose, identical, as far at least as can at present be made out, with ordinary *dextrose*." It is evident that a ferment other than the amylopsin connected with the digestive process must be the active one, and that it must reach the liver by a channel other than the intestinal tract, the villi, etc. Again, it must be very nearly similar to the salivary and pancreatic amylolytic ferments. The salivary glands are so remote anatomically that they can hardly be considered; we are brought, therefore, to the pancreas as the only organ which could act as source of a ferment or diastase having for its main function to convert glycogen into dextrin.

As shown by von Mehring, Minkowski, and de Dominicis, removal of the pancreas causes marked glycosuria, and this persists whether the animal be given carbohydrates or not. All the other symptoms of diabetes mellitus appear,—namely: increased flow of urine, considerable urea, acetone, etc.; great thirst and hunger, emaciation, marked muscular weakness,—followed by death in two to four weeks. Indeed, we are vividly reminded of the suprarenal glands, on ascertaining that grafting of a piece of pancreas in the abdomen or skin will arrest the glycosuria, and that, if a small portion of the organ is left, the symptoms will disappear. Again, whether carbohydrates are given as food or not, the glycogen disappears from the liver. "We may believe, from these experiments," says Howell, "that the pancreas produces a substance of some kind that is given off to the blood or lymph, and is either necessary for the normal consumption of sugar in the body or else, as is held by some, normally restrains the output of sugar from the

liver and other sugar-producing tissues of the body. What this material is and how it acts has not yet been determined satisfactorily." That we are dealing with an internal secretion is clear, and, such being the case, the secretion probably passes out into the blood by the pancreatic vein, which "opens into the splenic and mesenteric veins." As these open, in turn, in the portal vein, the pancreas would then supply a special ferment for the conversion of glycogen into a functional sugar.

If the foregoing symptoms are closely scrutinized, it soon becomes apparent that the functions of the pancreas—as will be shown in the next chapter—are far more important than is generally believed. For the present, however, we will limit our inquiry to the subject in point.

The fact that, notwithstanding the ingestion of carbohydrates, the glycogen will totally disappear from the liver is easily accounted for. A prominent function of the pancreas during intestinal digestion is to transform starches into maltose, to insure absorption of this sugar. When the organ is removed, therefore, its amylopsin is no longer furnished to the intestinal contents, starches are not properly converted, and the portal vein carries no maltose to the hepatic lobule. The production of glycogen, therefore, ceases. The fact, however, that we can so easily account for this phenomenon suggests that:—

1. The pancreas is the organ upon which all the preliminary functions connected with the formation of glycogen depend.

2. Its amylopsin converts starches in the intestine to prepare them for the elaboration of glycogen in the hepatic cell.

3. Its internal secretion, supplied to the portal system by way of the splenic vein, converts glycogen into dextrose.

That we are on the right path is suggested by a series of experiments by Croftan,[23] in which the conversion of glycogen into sugar was obtained by means of injections of suprarenal extract: "Incomplete as these experiments are," says the author, "they reveal the fact that the injection of suprarenal extract can cause the excretion of dextrose provided the quantity injected *is sufficiently large.* Why in the case of one

[23] Croftan: American Medicine, Jan. 18, 1902.

animal more must be given than in the case of another to produce approximately the same excretion is undecided and remains to be determined." Dwelling upon the presence in the adrenals of a diastatic ferment, he states that "two possibilities may present themselves, viz.: either the suprarenals manufacture a diastatic ferment or they retain the diastatic ferment that is formed elsewhere in the body (pancreas, salivary glands) when it is carried to them in the blood- or lymph- stream." The author also refers to the investigations of F. Blum,[24] who, "testing the effects of suprarenal extract empirically," discovered "glycosuria in 22 out of 25 animals that he operated on." Our interpretation of the manner in which these investigators reached their results is, of course, not that of Croftan, since, as we view the process, the oxidizing substance constitutes the active suprarenal agency as a compound of suprarenal secretion and oxygen.

We are dealing with enhanced physiological activity *somewhere.* Indeed, Croftan says: "In order that hyperglycosuria be produced the amount of sugar normally poured into the blood must be increased, or the amount normally destroyed must be decreased." That excessive activity was either procured by the injected extract or by overstimulation of the adrenals, both leading to total insufficiency, is shown by the brief history of one of the animals: "The second rabbit died in one hour and ten minutes; here some *spasmodic* symptoms, involving chiefly the *posterior* extremities, preceded the coma." Referring to two rabbits, including the latter, the first having died in two hours and forty minutes and to "all others to be spoken of presently" (six, all told), he says: "Dextrose was identified in the urine by its cupric-reducing powers and the phenylhydrazin test; in one of the dogs in addition by circumpolarization and yeast fermentation. The substance excreted was undoubtedly dextrose. The amount excreted would be far too large to be explainable by a splitting of the jecorin-like substance mentioned above; it would not, moreover, be possible for considerable quantities of dextrose derived from this source to appear in the urine for several days after the injec-

[24] F. Blum: Deutsche Archiv f. klin. Med., Oct. 31, 1901.

tion." Excessive stimulation by a great increase of oxidizing substance in the blood evidently occurred. As soon as the extract was injected it was carried to the lungs, and lost its individuality immediately therein by taking up oxygen. It could no longer, therefore, act as a diastase.

The question now to decide is this: General stimulation enhanced the production of an amylolytic ferment either by the liver or by the pancreas. To which organ can we ascribe this function? Since oxidation destroys sugar, a great excess of oxidizing substance in the blood would burn sugar actively on all sides and produce the *opposite* of glycosuria: *i.e.*, excessive combustion and rapid disappearance of the liver glycogen through abnormal use of it in the other organs. But here we have, as a result of a great increase of oxidizing substance in the blood, marked glycosuria, and that evidently without preliminary feeding, since this fact is not mentioned by Croftan. As the oxidizing substance does not affect glycogen, that of the liver could not be converted by it into sugar; hence the excessive production of the latter can only be accounted for by an equally excessive production of amylolytic ferment.

Claude Bernard showed that conversion of glycogen into sugar took place more rapidly when the blood was made to traverse the liver with unusual speed. Yet he attributed the formation of the ferment to the liver, having obtained it from pulp rubbed up and treated with glycerin, after the liver had been washed out so as to remove the vascular contents. But it seems clear that injections by the portal vein will hardly deplete the liver of every particle of the ferment in its minute lobular capillaries, while reduction of its substance to pulp and a three days' immersion in glycerin will dissolve all that contained in the latter. When we consider how readily conversion can be produced,—even by traces of soluble albumin, according to Seegen,—it is evident that upon the addition of water to the glycerin solution the very small proportion that may have remained imprisoned in some of the lobules will suffice for the conversion of glycogen.

One of Claude Bernard's experiments seems to us to afford proof that the amylolytic ferment reaches the liver through

the portal vein. By ligating the latter vessel he created a collateral circulation, and shifted the portal-blood stream into the general circulation. Ten or 12 grammes of sugar were then given to the animal, and sugar was soon found in the urine. In a normal dog, on the other hand, 50 to 80 grammes had to be administered before this result was obtained (M. Duval[25]). The absence of sugar in the latter animal's urine until a very large quantity of sugar had been ingested distinctly shows that conversion of its *glycogen* only occurred because its portal vein was open; in the other dog it was not converted glycogen that passed into the urine, but maltose, *i.e.*, intestinal starch which had been submitted to the action of the pancreas's intestinal ferment,—*i.e.*, amylopsin. If we now couple the fact that conversion of liver-glycogen only occurs when the portal vein is free with Claude Bernard's observation that increased speed of the portal blood through the liver causes the glycogen to be converted more rapidly, it seems clear *that the conversion process is not due to an hepatic ferment, and that the pancreas supplies, as an internal secretion, the ferment which converts glycogen into dextrose.*

A perplexing feature of all this requires elucidation, however. If, as we have stated, the blood-plasma contains an oxidizing substance, why is the sugar not oxidized on its way to the tissues of distribution? Armand Gautier[26] refers to the investigations of Jaquet, which demonstrated that sugars mixed with blood containing the oxidation ferment previously referred to, and which we found to be of suprarenal origin, did not become oxidized. He ascertained, however, that upon adding to the blood a small quantity of fine pulp of muscle, lung, or of any other organ, the oxygen was absorbed. This obviously indicates that *dextrose passes through the blood without being destroyed, and it can only become oxidized after combining with bodies produced by the organs to which it is distributed.*

General Functions of the Liver, Spleen, and Pancreas.—All the facts reviewed in this chapter suggest the following conclusions as to the functions of the liver, spleen, and pancreas:—

1. The hepatic artery, owing to the oxidizing substance that

[25] M. Duval: *Loc. cit.*, p. 378.

[26] Armand Gautier: "La Chimie de la Cellule Vivante," p. 98.

its plasma contains and the mode of distribution of its terminal capillaries, supplies the exogenous chemical energy which initiates and sustains all reactions in the hepatic lobule that require oxygen.

2. The nervous supply of the liver is composed, first, of terminal subdivisions of the general motor system (splanchnic-sympathetic), which furnish nervous energy during the passive stage of functional activity by insuring tonic contraction of all vessels, and, second, of terminal subdivisions of the vagus, which excite and govern the active stage of functional activity by regulating the caliber of the hepatic arterioles and by supplying nervous energy to the hepatic cells.

3. In the normal subject the liver is anatomically isolated from structures that come into contact with bacteria, and protected against their intrusion by the bactericidal products of the intestinal glands and follicles.

4. The capillaries of the hepatic lobules, owing to the admixture therein of the hepatic artery's oxidizing substance with the portal vein's waste-laden blood, are the seat of several functions now ascribed to the hepatic cell.

5. Blood-pigments and iron, derived from the intestine and spleen, simultaneously penetrate the hepatic lobule, and combine with the oxidizing substance therein to form hæmoglobin. The uncombined pigment is eliminated with the bile as bilirubin.

6. Urea is the end-product of three successive reactions, viz.: (1) nitrogenous bodies are reduced to amides in the afferent veins, —mesenteric and portal; (2) the amides are dissociated into ammonia, carbonic acid, and water by the oxidizing substance in the hepatic lobule; (3) urea is formed by synthesis in the efferent veins,—hepatic and vena cava.

7. The hepatic cell contains, besides its vacuoles and nuclei, numerous canaliculi (Schäfer) and a vesicular vacuole which opens into the bile-capillaries by a canaliculus (Kupffer); the canaliculi and the vesicular vacuole are probably connected.

8. Glycocholic acid and taurocholic acid are functional acids, inasmuch as they dissociate and appropriate waste-products, and, under the influence of the oxidizing substance, convert them into excrementitious products in the canaliculi of the hepatic cells.

9. The waste-products so converted by the biliary acids and the latter themselves, constituting bile, are transferred, along with

other products for which the latter may serve as vehicle,—bilirubin, earthy salts, etc.,—to the vesicular vacuole of the cell and eliminated by the canaliculus that opens into the bile-capillaries.

10. The biliary acids, blood-pigments, iron, and other bodies or any of their components, that may prove useful to the organism are, entirely or in part, reabsorbed by the intestinal venules and returned to the portal circulation.

11. The sugars converted from intestinal foodstuffs in the intestines are brought to the hepatic lobule with the portal blood, and penetrate the canaliculi with the latter and with the oxidizing substance. During the bile-forming reaction the sugars are dehydrated, and, probably with the assistance of the cellular protoplasm, converted into glycogen.

12. The liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas as an internal secretion, which enters the portal circulation by the splenic vein.

13. Dextrose is distributed to the organs in which it is used as a source of energy by the blood, and only becomes vulnerable to oxidation when combined with products of metabolism furnished by those organs.

CHAPTER VIII.

THE INTERNAL SECRETIONS OF THE PANCREAS AND SPLEEN.

Glycosuria and Overactivity of the Adrenal System. —The pancreas and spleen are considered together because there is considerable evidence in favor of the view that they are functionally associated; and it is to give the analysis of this question and its relationship with the ferments furnished by the pancreas to the portal blood due prominence that we have, under other headings, considered the better-known functions of both organs.

To sustain our belief that liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas which penetrates the portal vein directly,—*i.e.*, by way of the splenic vein,—we were fortunate in having at our disposal the experiments of Croftan, which showed that suprarenal overactivity could so augment the functional activity of the ferment-producing organ as to induce a very great increase in the sugar eliminated. This feature requires further study, since it will tend to elucidate other functions of the pancreas.

We believe that we have conclusively shown that drugs of various kinds increase the functional activity of the adrenals. The uniformity of the phenomena traceable to these glands under the influence of such agencies seems to us to warrant the conclusion that, if we can demonstrate that glycosuria is also subject to the latter, its fluctuations following those of the suprarenal activity or insufficiency induced by them, a direct connection between glycosuria and suprarenal overactivity will have been shown. Yet we must bear in mind, in this connection, that all active drugs *may* have a primary action upon tissues for which they possess a specific affinity before the suprarenal protective functions are fully awakened. We have seen that even electrical stimulation of the splanchnic is only followed by vermicular motions of the intestinal wall after some time has elapsed. But too much weight must

not be given this feature, inasmuch as we have personally seen the typical symptoms of total suprarenal insufficiency occur in a dog within twenty seconds after a fatal dose of hydrocyanide of potassium had been administered. Large quantities of the less active drugs are more likely to reach the tissues for which they possess a special predilection, bromide of potassium, for instance, than such an agent as that previously mentioned. While, therefore, we cannot say that excessive formation of sugar, when drugs are given, is due only to overstimulation of the adrenals, we can say that all drugs can produce it when they stimulate suprarenal activity. Furthermore, it seems probable that some drugs not only do this, but they likewise, owing to their affinity for certain tissues, enhance the production of sugar by increasing the functional activity of the intimate structures of the organs concerned in its production from ingested substances—thus stimulating two different sets of organs simultaneously. Such an agent we probably have in phloridzin.

In an able and exhaustive review of the subject of toxic glycosuria, F. Cartier,[1] of Paris, says: "The symptomatology of phloridzin is very limited, seeing that it does not give rise to a true intoxication. . . . In man it is even possible to bring on glycosuria, and maintain it a long time, without giving rise to general disorders, provided a copious alimentation is insured." We have evidence in the last sentence that the main general result is an *excessive formation* of sugar, and, more carbohydrates being required, it is to an excessive production of the converting agent that we must ascribe this phenomenon. Still, if general symptoms are absent, what becomes of the suprarenal overactivity? Cartier answers this question when he says: "Yet *all* authors who have studied phloridzin unite in saying that the animal experimented upon becomes *voracious*, and, if not overfed, rapidly wastes. . . . When alimentation is insufficient, grave phenomena appear. Phloridzinic glycosuria has been obtained in animals entirely deprived of hydrocarbons; under these circumstances general symptoms *analogous to those of diabetic coma* have been observed."

[1] F. Cartier: Thèse de Paris, 1891.

Osler[2] states that Frerichs recognized three groups of cases; two of these are of special interest to us: *(a)* Those in which after exertion the patients were suddenly attacked with weakness, syncope, somnolence, and gradually deepening unconsciousness, death occurring in a few hours. *(b)* Cases with preliminary gastric disturbance, such as nausea and vomiting, or some local affection, as pharyngitis, phlegmon, or a pulmonary complication. In such cases the attack begins with *headache,* delirium, great distress, and *dyspnœa,* affecting both inspiration and expiration: a condition called by Kussmaul *air-hunger. Cyanosis* may or may not be present. If it is, the *pulse* becomes *rapid and weak* and the patient gradually sinks into *coma,* the attack lasting from one to five days. The need of a copious supply of carbohydrates obviously points to increased oxidation. Indeed, complete absence of glycogen in the liver and muscles has been noted. The voracious appetite and rapid wasting further sustain this —and simultaneously, therefore, the presence of suprarenal overactivity. The italicized words in the list of terminal symptoms, on the other hand, as prominently point to the gradually deepening suprarenal insufficiency.

Alluding to the effects of acids in the production of glycosuria, Cartier refers to the experiments of Pavy[3] with phosphoric acid. An increase of sugar was noted in twenty minutes; fifteen minutes later a large quantity was present. In another strong, but *fasting,* dog the sugar was markedly reduced by a smaller dose. Hæmorrhagic infiltration of the gastric and intestinal tissues and hæmaturia were also noted. These are all familiar landmarks of suprarenal origin. Striking, in this connection, are the observations of Stadelmann,[4] who found that the production of CO_2 decreased in the rabbit during acid intoxications as it does in diabetic coma. In a foot-note Cartier says: "Voit and Pettenkofer and Gaethgens have peremptorily shown, by means of most precise experiments, that (1) the oxygen absorbed by a diabetic is much less than by a normal man, and that it decreases progressively until

[2] Osler: "Practice of Medicine," third edition.
[3] Pavy: Guy's Hospital Reports, vol. of 1861.
[4] Stadelmann: Deutsche med. Wochenschrift, Nov. 4, 1890.

the end of the disease, when it is hardly equal to half of the normal quantity; (2) that the CO_2 exhaled is likewise reduced." That this is essentially due to suprarenal insufficiency—*i.e.*, reduced oxidation—is shown by the fact that, in a case of coma due to meningitis witnessed by Stadelmann, the proportion of CO_2 was 28.2 per cent.; while in diabetic coma the gradual decline is that observed in Minkowski's rabbits, which, from the normal 25 per cent., steadily dropped to 16, 8.8, then 2.9 per cent.

We have seen that tetanus was due to excessive suprarenal activity. Cartier refers to the experiments of Claude Bernard, which showed that strychnine produced glycosuria in dogs. "It is unnecessary to reproduce here," says Cartier, "the symptoms of poisoning produced by this alkaloid; we will simply say that nothing recalls tetanus to such a high degree as does intoxication by it." We have another proof that it is due to an excessive production of a ferment or some other agency possessed of converting powers since Langendorff found that "glycosuria only occurs in frogs when the liver contains glycogen. . . . In the summer, when their liver contains none, strychnine does not cause diabetes in these animals."

We are reminded of the disorganization of hæmoglobin produced by advanced suprarenal insufficiency when, referring to curare glycosuria, Cartier says: "Others account for this glycosuria by an insufficiency of the respiration and by slowing of combustions. The dark coloration of curarized blood indicates this asphyxia." Even the nervous distribution, *as we interpret it,* including the connection between the anterior pituitary body and the adrenals, finds itself sustained in a remarkable manner by the following lines of Cartier's in reference to morphine glycosuria: "An extremely interesting fact that all these investigations indicate is that one can produce with a toxic substance exactly similar phenomena to those recorded by Claude Bernard in his lessons at the College of France, and obtained by puncture of the medulla, and that these toxic glycosurias can in most cases be arrested, as are glycosurias of nervous origin, by severing the centrifugal nerve-impulse conductors. Indeed, section of the pneumogastric (centripetal nerve) does not prevent glycosuria caused either by Bernard's puncture or by morphine; but, on the contrary,

section of the splanchnic nerves (centrifugal nerves) and of the medulla above the origin of these nerves prevents both the experimental diabetes of Claude Bernard and the toxic diabetes caused by morphine."

The list of drugs that are able to produce glycosuria could be indefinitely prolonged: it includes all those that produce suprarenal overactivity. But this does not mean that the ferment-producing organ is alone stimulated; glycosuria is but one of the manifestations of the exaggerated *general* metabolism induced, and oxidation processes are enhanced accordingly. Toxic glycosuria, therefore, only represents the surplus of sugar which oxidation processes have not consumed; the excess of sugar actually produced is probably far greater than the surplus which the urine shows. Again, certain drugs —phosphorus, for instance—do not produce glycosuria to any marked degree; as soon as the dose capable of causing it is reached, the adrenals lapse into insufficiency, and, if the dose is pushed to any extent, even the normal ratio is reduced. Antipyrin is now considerably employed in diabetes; we have seen that this drug and acetanilid readily produced suprarenal insufficiency and dissociation of the hæmoglobin molecule. This is sufficiently extensive sometimes to manifest itself as methæmoglobinuria or even hæmatoporphyrinuria. All these facts seem to us to indicate that *toxic glycosuria is primarily due to overstimulation of the adrenal system, the excessive functional activity which increased oxidation produces giving rise to an inordinate production of an agency that converts glycogen into sugar.* All these features will again be reviewed.

That the agency which converts glycogen into sugar is the amylolytic ferment produced by the pancreas to which we have referred is further sustained by the foregoing facts, especially in view of the amylolytic properties of the pancreatic secretion in the intestine. Since the conversion into sugar occurs during fasting as well as during digestion under the effects of toxics, the reaction can only include the hepatic glycogen and pancreatic ferment; and, there being nothing in the intestine to convert during fasting, the ferment must necessarily reach the glycogen by another channel. *May this not be the more direct route afforded by the splenic vein?*

Yet there is a possibility that the flow of amylopsin in the intestine, which the enhanced activity of the pancreas must undoubtedly increase, may be reabsorbed by the venules, and, being carried into the portal system, produce conversion of the glycogen precisely as if it had entered the portal vein by the way of the splenic vein. But we have seen that, while removal of the pancreas is rapidly followed by death, very large portions of the gland can be safely removed. Admitting that the operators may have left the portions related with the pancreatic duct, how could we account for the effects of transplanted fragments in arresting the glycosuria caused by removal of the pancreas, recorded by Minkowski[5] and Hédon?[6] As long as fragments transplanted subcutaneously remained normal no glycosuria occurred; it reappeared, however, when these fragments became histologically impaired. It is evident that the only channel here for the amylolytic ferment produced could be the blood. Thus carried to the heart, it then penetrated the liver by way of the hepatic artery, and reached the intercellular capillaries and the glycogen precisely as if it had penetrated the organ by way of the portal vein. Although but a small quantity of the ferment could thus reach the liver, it was evidently sufficient to convert the amount of glycogen required to build up the very limited proportion of sugar found in the normal blood, as previously shown. Again, we have seen that the product of intestinal reduction is maltose, while the urine of Croftan's animals when stimulated with suprarenal extract gave dextrose in very great quantities: a feature denoting successive processes. This and the other facts adduced appear to us to contribute additional evidence to the view that *the dextrose-forming ferment enters the portal system by way of the splenic vein.*

THE FUNCTIONAL RELATIONSHIP BETWEEN THE PANCREAS AND SPLEEN.

The internal secretion of the pancreas and that of the spleen may perhaps be best studied by submitting to a careful analysis the hypothesis advanced by Schiff, sustained by

[5] Minkowski: Verhandl. d. XI Congr. für Inn. Medicin, Wiesbaden, 1892.
[6] Hédon: Archives de Physiologie norm. et path., vol. iv, 1900.

Herzen,[7] and defended by Lépine[8] and others that the spleen supplies a ferment which, when added to pancreatic juice, greatly increases its digestive energy. Schiff believed that the splenic substance played an important part in the genesis of the pancreatic proteolytic ferment, but Herzen attributed to it the function of converting trypsinogen into trypsin, the albumin-solving constituent of the pancreatic juice. This subject was more recently studied experimentally by Gachet and Pachon,[9] who were led to conclude, as previously suggested by Laguesse (1893) and Schäfer (1895), that the spleen furnishes a true internal secretion which possesses a special affinity for the pancreas, the protrypsin of which it transforms into trypsin, as suggested by Herzen. This substance loses its properties at the boiling-point; is precipitated, when in aqueous solution, by alcohol; and is, therefore, of the nature of a ferment.

Lépine also confirmed Schiff's and Herzen's view by experiments *in vitro* and by blood-analyses. He found that a mixture of pancreas and spleen-pulp in glycerin possessed far more active properties than pancreas alone similarly prepared. On the other hand, the blood of an animal deprived of its spleen proved almost inert as a tryptic, while the blood of a normal dog possessed distinct digestive powers. Analysis of the experiments of these various authors distinctly indicates that some function of the kind mentioned exists. The anatomical relations of the organs involved, however, make it impossible for the internal secretion referred to, to penetrate the circulation without first passing through the liver *with the blood of the splenic vein, which collects the pancreatic internal secretion and carries it to the portal vein.* This fact seems to suggest that, besides the amylolytic ferment, the portal carries a ferment to the liver calculated to insure the tryptic action upon albumins and kindred bodies. If we consider that we have in the blood of the portal channels all the products of digestion and that trypsin is "applied solely to albuminoid

[7] Herzen: Revue Générales des Sciences pures et appl., vol., 1895.
[8] Lépine: Société des Sciences Médicales de Lyon, July, 1895.
[9] Gachet and Pachon: Archives de Physiologie, April, 1898.

conversions and changes" (Charles), the importance of the spleen's internal secretion will appear.

Albuminoids, especially those ingested with food, are not the inoffensive bodies that they appear to be; indeed, they constitute the foundation of some of the most dangerous substances that enter the organism when their molecular structure undergoes certain changes. Apart from any function of the spleen in the direction mentioned, the pancreatic trypsin supplied to the intestine—if we can judge by the manner in which a small remnant of pancreas will prevent glycosuria—must persist even when the pancreas is in a state of advanced disease. We saw that one-twentieth of the functional area of the adrenals sufficed to sustain the general oxidation processes. That the pancreas possesses at least four times more functional area than it absolutely needs has been experimentally demonstrated. With proper—fresh, uncontaminated—food, a normal organism is practically invulnerable, so splendidly is it armed against any chemico-physical decomposition that the ingesta may undergo. But these physiological defenses may be weakened through general or local adynamia, *i.e.*, lowered oxidation processes, and peptones, capable of yielding *toxalbumins, leucomaines, ptomaines,—all* albuminoids,—fail to undergo further splitting in the intestinal canal. Again, and under the same circumstances, notwithstanding the destructive action of the gastric and intestinal secretions, bacteria and their toxins may penetrate the debilitated villi and the portal circulation. The blood-stream, furthermore, may be invaded through peripheral organs not only by bacteria and their *toxins*, but also by *vegetable poisons* and venoms: *all* albuminoid substances, as previously emphasized. Even these do not represent all the sources of danger that a protective function, such as that represented by the pancreatic and splenic secretions, would have to meet, were they, as we believe, mainly intended to fulfill such a mission.

If toxic albuminoids reach the portal vein by way of the intestinal villi and the mesenteric veins, all conditions therein are most advantageous for the action which trypsin is known to exercise upon them: It acts with great energy in alkaline media, and the presence of oxygen does not inhibit its action;

if, therefore, the venous blood of the afferent channels should happen to contain an unusual amount of oxidizing substance through suprarenal overactivity, the tryptic disruption of peptones would not, to say the least, be prevented; in laboratory experiments the need of an antiseptic when pancreatic juice is used is well known; we have seen that in the afferent vessels, the fluids derived from the intestines had been saturated therein with the antiseptic secretion of the glands of Brunner and Lieberkühn, and it is evident that their influence would normally continue in the venous channels; finally, the action of trypsin does not cease when the peptone stage is reached; it converts these into leucin, tyrosin, aspartic acid, etc., the fate of which derivatives we have traced down to urea, the end-product eliminated in the urine.

The rôle played by the spleen in the pancreatic digestion of proteids, and to which we add a prophylactic function, has been so ably reviewed by H. F. Bellamy in a comparatively recent number of the London Lancet[10] that we will utilize the greater part of his paper to illustrate the various features that appear to us to furnish a solid foundation, not only for the views of Schiff and Herzen, but also for our own.

The author reviews the history of the question as follows: "Corvisart found that in dogs in full digestion there was for a certain time a constant rise to maximum in the digestive power of the pancreatic juice, succeeded by an equally constant fall to minimum. The maximum was attained during the eighth hour after the ingestion of a meal, the minimum from the thirteenth to the eighteenth hours. Meissner announced that in fasting animals the pancreatic juice possessed little or no peptonizing power. Schiff, after a number of experiments on such animals as rats, guinea-pigs, rabbits, and young dogs or dogs of small breed, found that during fast the pancreas really possessed almost no peptonizing power; the albumin imprisoned in the duodenum remained there for whole hours without dissolving, the infusion of the gland giving results equally negative. On the other hand, in the case of ravens and adult dogs of large breed the pancreas preserved during fast a certain digestive power, even in animals in a condition

[10] H. F. Bellamy: London Lancet, Oct. 27, 1900.

of complete fast which had digested a copious meal the day before; under these circumstances, indeed, the infusion of the whole pancreas of a large dog was capable of digesting from 50 to 60 grammes of albumin. In such dogs this condition of weak digestion was maintained until toward the fourth hour after the meal, after which time digestion proceeded very much more rapidly, so that at the time of maximum the pancreatic infusion was capable of digesting from 50 to 60 grammes of albumin. As regard cats and small dogs, he was able to confirm the results of Corvisart. By these experiments, then, the above-mentioned observers succeeded in establishing the following two facts: (1) that the activity of the pancreatic juice or of an infusion of the gland is not continuous, but intermittent, and (2) that maximal activity appears regularly during the culmen of gastric digestion (from six to eight hours after a meal), at which time it is very considerable."

Passing now, for the moment, from the pancreas to the spleen, he proceeds briefly to examine the behavior of this organ in relation to digestive phases. "Lauret and Lassaigne in 1825 discovered that the spleen began to become congested at the moment when the stomach discharged chyle abundantly into the duodenum; that this is, however, merely a coincidence is shown by the fact that the congestion also occurs after ligature of the pylorus. Dobson in 1847 discovered that in a dog three hours after a meal the spleen is still as small and as anæmic as during fast; that it commences to dilate in the fourth hour after a meal; that five hours after it has attained its maximal turgescence, decreasing afterward from the seventh hour to attain toward the twelfth its minimal volume. Landois in the same year found that in the rabbit the relative weight of the spleen to the body-weight of the animal was the same two hours after a meal as after forty-eight hours of fast; that it increased considerably from the fifth hour, remaining high until the twelfth hour. . . . . .

"The striking synchronism in the splenic congestion and the presence of trypsin in large quantity in the pancreatic juice or in an infusion of the gland was observed by Schiff and caused him to repeat all his former experiments on the tryptic digestion of albumins, this time on animals in which the spleen

had been for some time removed and on others in which it was prevented from dilating by ligature of its hilum at the time of the experiment. He experimented in this way upon a very large number of dogs and cats; nearly all his experiments were double: *i.e.*, performed at the same time and in the same manner on two animals selected so as to resemble one another as much as possible, and in only one of which had the spleen been extirpated or ligatured. These experiments were of two kinds: (1) those conducted with pancreatic infusions, and (2) those carried out in the living duodenum, the following being typical examples:—

"*I. Infusions. Ligature of the Hilum of the Spleen.*—Two cats, after fasting for 19 hours, received as much meat as they would eat; 1 hour afterward they were etherized, and the spleens, which were found to be in a state of contraction, were brought out through a wound in the abdomen and their hila were encircled by strong thread; in one of the animals the hilum was firmly tied, but in the other it was simply encircled and a knot was tied, leaving the splenic circulation perfectly free (this was done in the endeavor to equalize traumatic conditions as much as possible). The spleens were then replaced in the abdominal cavity and the wound was sutured. On recovering from the anæsthesia the animals did not appear to suffer. They were killed 6 hours later. Gastric digestion was found to be more advanced in the animal in which the splenic vessels were tied; the pancreas of both was cut up into small fragments and infused with 100 cubic centimeters of water for an hour at 35° C.; the liquid was afterward decanted and returned to the warm chamber together with cubes of albumin.

"*Result.*—In 7 hours the pancreatic infusion of the cat in which the hilum was not ligatured digested 17 grammes of albumin; that of the other did not digest at all even at the end of 12 hours.

"This experiment was performed on a large number of cats and dogs and always gave the same result. In spite, however, of the perfection of gastric digestion in the operated animals, it was possible to lay at the door of traumatism the absence of duodenal digestion; to correct this the experiment was repeated as follows:—

"*Extirpation of the Spleen.* — Two dogs—one normal, the other having undergone splenectomy a month previously, but at the time of the experiment in perfect health—were operated upon, while fasting, as follows: Etherization, ligature of the pylorus, injection into the stomach, per œsophagus laid bare and opened, of 50 grammes of peptone and 2 grammes of dextrin; to allow drainage of swallowed saliva the œsophagus was ligatured below the opening. Both animals were killed five hours later, and each pancreas was infused for three-fourths of an hour in 100 cubic centimeters of water at 35° C. Although death had occurred before the most favorable moment for the experiment,—*i.e.*, in advance of the summit of the splenic curve,—the infusion coming from the dog with the spleen intact digested 17 grammes of albumin in 17 hours, while the other digested nothing even in 18 hours. Numerous experiments made in this manner always gave the same result. The spleenless dogs had in many cases undergone splenectomy several months before the experiment, and the determination in them of perfect conditions of health was always a matter of great care.

"*II. Experiments in the Living Duodenum. Ligature of the Duodenum at Both Ends.*—Two dogs after fasting for 17 hours received as much meat as they would eat and immediately afterward were operated upon as follows: Etherization, laparotomy, ligature of the pylorus and of the bile-duct, introduction into the duodenum of from 30 to 40 grammes of albumin, and ligature of the jejunal end. In one of the animals the splenic hilum was also ligatured. Both were killed 7 hours later.

"*Result.*—In the dog with the splenic hilum tied the albumin was found to be intact; it had, however, disappeared in the other.

"This experiment was also several times repeated on animals which had undergone splenectomy a long time previously, and always yielded the same result; it is, of course, capable of being combined with the preceding by making an infusion of the pancreas after the death of the animals. Such infusions give results in harmony with those furnished by the duodenum itself. Further, it will be remembered that in the pancreatic

juice of dogs of large breed Schiff generally found, even while fasting, a certain quantity of trypsin; when the same were spleenless, however, he was unable to find any.

"*Digestion in the Normal Duodenum Provided with a Fistula.*—A duodenal fistula was established in a dog. After complete recovery a measured and constant quantity of albumin was introduced every day into the duodenum inclosed in a small envelope of fibrous membrane fixed to the cannula by a thread some centimeters long. The progress of digestion was then observed, the following results being obtained: 1. When the animal was fasting the albumin took from 5 to 6 hours to become dissolved. 2. When the albumin was introduced into the duodenum during the 2 to 3 hours immediately following the ingestion of a meal by the animal it remained unchanged. 3. When introduced 4 hours after a meal it disappeared very quickly,—in about half the time, in fact, occupied during fast. These facts having been duly noted, the spleen was then extirpated, and after complete recovery the same experiment was repeated; very different results were now obtained. Whether fasting or in full digestion the time taken for the digestion of the albumin was exactly the same, viz.: from 5 to 6 hours. The acceleration in the peptonization which had formerly appeared after the fourth hour of digestion, and which coincided both with the appearance of trypsin in the pancreatic juice and with the dilation of the spleen, was now absent. The slow digestion (from 5 to 6 hours) in this experiment was probably entirely due to the secretion of the duodenal glands, which possess only a very feeble digestive power; the active, rapid digestion was due to the appearance, in large quantity, of trypsin in the pancreatic juice: a phenomenon wanting in the spleenless animal. . . . Schiff endeavored to interpret the facts by the following theory: During the congestion of the spleen a substance is produced within it which, carried away by the blood, gives to the pancreas the wherewithal to form its peptonizing ferment. . . . In 1872, however, the theory of Schiff received a rude shock through the great discovery of the zymogens by Heidenhain and his pupils. From the researches of this observer it appeared that, as the gastric mucous membrane forms at the

outset hardly any active pepsin, but a zymogen accumulating in its glands in the intervals of digestion, so the pancreas does not at once elaborate active trypsin, but a substance destined to become trypsin under certain conditions and in a certain phase of the digestive act, this substance being, of course, the pancreatic zymogen trypsinogen, or protrypsin. The researches of Heidenhain are well known, and it suffices to recall here only one or more essential points: Thus from them we know that the pancreas of a fasting dog contains little or no trypsin, but merely trypsinogen; consequently its glycerin infusion possesses little or no digestive power; the infusion, however, of a dog in full digestion digests rapidly and copiously, because it contains trypsin. If the pancreas of a fasting dog be divided into two equal portions, one of which is infused at once and the other only after an exposure of 24 hours to the air, the first is found to be inactive, while the other is immediately and energetically active, from which it is clear that the inert trypsinogen which it contains becomes spontaneously transformed into active trypsin; indeed, it suffices to pass a current of oxygen through a pancreatic infusion, rich in trypsinogen and poor in trypsin (an active infusion), to transform it into an infusion possessing a digestive power. This transformation, then, is an oxidation, trypsin being oxidized trypsinogen.

"The fact observed by Heidenhain of the continuous formation and storing up of trypsinogen in the pancreas and its subsequent transformation into trypsin during the culmen of gastric digestion proved that the former substance at any rate enjoyed an origin quite independent of all influence outside the pancreas itself, and the hypothesis of Schiff as to the intervention of the spleen seemed, in consequence, to be at fault. But it was only the theory of Schiff which suffered by these new revelations; as far as the experimental results of the two observers were concerned, physiologists were face to face with two series of apparently contradictory facts—apparently because facts properly observed can never stand in contradiction with one another, and when they appear to do so it is merely because the interpretation of them is either false or incomplete. It fell to the lot of M. Herzen to unravel the tangled hypotheses. It appeared to him that, by modifying the hy-

pothesis of Schiff as to the manner in which the spleen acts as a tryptogene, a fusion of the respective facts of Schiff and Heidenhain could be brought about, and that, far from being antagonistic, they could be shown to be reciprocally corroborative. He argued thus: since the zymogen, even in splenectomized animals, is being continuously elaborated, and therefore independently of the spleen and its periodical congestion, and that it accumulates in the gland-cells during fast, but that it becomes rapidly and copiously transformed into trypsin only in the presence of the spleen and in direct proportion to its dilation, it would seem feasible that the spleen produces, by 'internal secretion' during its congestion, an unknown substance, which, carried away by the circulating blood, transforms the inert zymogen already deposited in the pancreas into active trypsin destined to pass into the secretion of the gland, and that the influence exercised upon the zymogen by this product of the spleen seemed to be a condition *sine qua non* for the transformation of the former into trypsin, at least in the living pancreas, since in the dead organ or its infusion it is so transformed by direct oxidation. This hypothesis of Herzen would seem to be further confirmed by the fact gleaned from the researches of both Schiff and Heidenhain, to wit: that the holding in zymogen of the pancreas at a given moment either of fast or digestion is always in inverse ratio to its holding in trypsin, and *vice versa*, while the latter is always in direct proportion to the spleen dilation.

"So far so good. But Herzen reasoned further. If the spleen really produces, during its congestion, a substance which brings about the transformation of the pancreatic zymogen into trypsin, it would then be possible to seize upon this substance in the spleen itself while in its turgescent condition (from 6 to 7 hours after a meal), and by at once making an infusion of it and mixing a certain quantity of this splenic infusion with pancreatic infusion made from the pancreas of a fasting animal (very rich in zymogen and very poor in trypsin, and consequently nearly inactive) there could be obtained *in vitro* a rapid and copious formation of trypsin easily recognizable by the amount of proteid digested in a given time. The control experiment would also be very simple, consisting merely

in mixing with the same pancreatic infusion that of a contracted and anæmic spleen, in order to observe whether it would have the same effect as that of the spleen dilated and engorged with blood. Artificial digestions actually carried out with these infusions gave enormous differences: whereas the pancreatic infusion alone, or that mixed with infusion of contracted spleen digested nothing or almost nothing, the same pancreatic infusion to which had been added infusion of engorged spleen digested rapidly and copiously; indeed, it had often completely digested its dose of proteid by the time that the other two, if digesting at all, had barely commenced. The mixed infusions thus behaved in the same way as a pancreatic infusion taken at the culmen of digestion.

"A large number of similar experiments were made with aqueous boric and glycerin infusions, each being double: *i.e.*, performed in two separate series of vessels, the one containing finely divided fibrin and the other equal-sized cubes of coagulated albumin. The results were always the same. . . .

"At the German Congress of Medicine held at Strasburg in 1886 Herzen exhibited several graduated flasks containing the residua of fibrin and albumin in a number of his digestions, the digesting liquid having been decanted and replaced by alcohol. The physiologists who examined them all recognized that the difference between the residua left by the pancreatic infusions alone and those of the mixtures of the pancreatic and splenic infusions were very obvious. In a private conversation with Herzen, however, Heidenhain made the following criticism: It is well known that the pancreatic zymogen is very greedy of oxygen; on the other hand, the spleen during its dilation is engorged with blood. The splenic infusions exhibited were intensely colored by dissolved hæmoglobin—*ergo*, the undoubted and considerable acceleration in digestion obtained by adding such a liquid to another containing trypsinogen could be quite simply explained by the rapid oxidation of the zymogen at the expense of the hæmoglobin. This objection disconcerted Herzen in no inconsiderable degree, and he lost no time in making it the subject of experimental inquiry. He at length succeeded in disproving it by the following excellent experiment: The pancreas of a normal fasting dog

was infused in pure glycerin and the infusion was divided into eight equal portions. These eight portions were mixed with eight samples of blood received directly into a double volume of glycerin, of which four came from a fasting dog and four from a dog in full digestion with the spleen greatly dilated. The four samples were taken in both animals from (1) the femoral artery, (2) the femoral vein, (3) the splenic artery, and (4) a large splenic vein. The eight portions were then given the usual dose of fibrin and placed at a temperature of 40° C. Now, it is evident that the femoral and splenic arterial blood of the two animals contained more oxygen than their venous blood; the former, then, according to Heidenhain, should exercise a powerful influence on the digestion, equal in the two dogs. On the other hand, according to Herzen, the splenic venous blood alone should exercise this influence and especially that of the digesting animal. The result of the experiment was as follows: After one hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic venous blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the digesting dog; the fibrin had almost entirely disappeared under the influence of the splenic venous blood of the same animal.

"The answer could not be clearer: the product of the internal secretion of the spleen, borne therefrom by the circulating blood, is present during the period of the dilation of the spleen in feeble, but appreciable, quantity in the blood of the general circulation and abundantly in the splenic venous blood. The venous blood returning from the contracted spleen only contains it in very small quantities. This experiment, several times repeated, always gave the same result, showing that it is not the blood as such which favors the transformation of pancreatic zymogen into trypsin, but that, by picking up from the spleen the unknown substance possessing this property, the blood becomes its vehicle and means of communication with the pancreas.

. . . . . .

"From the bulk of evidence collected by Herzen there thus seems to be very little room for doubt that, apart from hæmatopoietic, and possibly allied, functions possessed by the spleen, the organ furnishes a product of 'internal secretion' which causes in the pancreas the transformation of its inert zymogen into active trypsin."

Bellamy closes his article with a review of the criticisms to which the researches of Schiff and Herzen have been submitted. In the experiments of Lussana, in 1868, the spleens of three dogs were removed and the animals were subsequently killed to ascertain whether the extract of their pancreas would digest coagulated albumin. The pancreatic infusion of the glands of two of the dogs digested 0.25 gramme of albumin in 24 hours; that of the third digested 1.10 grammes in the same period of time. "The latter animal had, however, been killed three hours after a meal: *i.e.*, at a moment when, even had it been in possession of its spleen, that organ would not yet have commenced to become congested. The experiment, therefore, gave the result which might be expected,—viz.: no digestion,—for nobody would accept seriously the digestion of 1.10 grammes, knowing that the pancreas of a dog when digesting can dissolve from 50 to 60 grammes of albumin. . . ." Indeed, the experiments of Lussana appear to us to be confirmatory of Schiff's and Herzen's views.

Carvallo and Pachon also reported negatively, but, errors in their experimental procedures having been brought to their attention by Herzen, subsequent experiments caused Pachon and a new collaborator, Gachet, to reach the conclusions sustaining the views of Schiff and Herzen to which we have referred on page 368. "Nay, they did more," says Bellamy; "they invented an entirely new experiment, at once original and ingenious, which consisted in realizing *in vivo* what Herzen had hitherto only done *in vitro*. This experiment was as follows: A dog, which a long time previously had undergone splenectomy, was anæsthetized and half its pancreas was removed and immediately infused; at the same time a normal dog, in the height of digestion, was killed and its congested spleen was infused in water, and this infusion was injected into the venous system of the spleenless dog; from 15 to 20

minutes afterward the remaining half of the pancreas of the latter dog was infused exactly like the first; of the two infusions when given fibrin and albumin, the second only digested rapidly and copiously."

The investigations of Popelski are next reviewed. "In both normal and splenectomized cats," says Bellamy, "he collected the pancreatic juice by means of a cannula introduced into the duct of the gland, and was unable to find any difference in digestive activity. As, however, his cats had been fasting since the day before, his experiments were made outside the digestive period during which the spleen, becoming congested, furnishes abundantly its product of internal secretion which transforms rapidly and copiously the zymogen into trypsin." . . . "But Popelski also performed some analogous experiments on a dog with a permanent pancreatic fistula, made according to the method of Pawloff. The pancreatic juice of this animal was several times collected and examined before and after splenectomy without any difference in activity being demonstrable. This result, however, elicits no surprise in view of the fact that in both instances the juice was always collected immediately after a meal—*i.e.*,—again to repeat it—in advance of that digestive period during which the spleen enters into function and the pancreas abounds in trypsin; so that as well in this experiment as in that with his cats, Popelski was placed in that position in which the presence or absence of the spleen was a matter of perfect indifference. . . ." The discussion of the various features in point have led to considerable acrimony, but the impartial observer cannot fail to consider that the position of Herzen, of those reviewed, is the only tenable one.

In an article written since Bellamy's review was published Popelski[11] reiterates his views, and states that since it has been demonstrated that there exist in the organism *bodies in the nature of ferments possessing oxidizing properties*, which he believes to be derived mainly from leucocytes, the results obtained by Schiff, Herzen, Pachon and Gachet can all be explained by their action. During the height of digestion

[11] Popelski: Vratch, Feb. 3, 1901.

digestive leucocytosis prevails, and, an accompanying destruction of these cells yielding more oxidizing bodies, the latter, he thinks, are the source of conversion of protrypsin or trypsinogen into trypsin, which thus becomes a function of the blood. Thus, the spleen would have nothing to do with the process, the hyperæmia and dilation of this organ during the formation of trypsin being regarded merely as concomitant phenomena.

The only feature of interest to us in Popelski's last paper is the fact that his experiments were performed in accordance with the directions of Schiff. That he should be driven thereby to ascribe all the phenomena witnessed to the action of "oxidizing bodies" adds materially to the data contributed by Schmiedeberg, Jaquet, Abelous and Biarnés, and Salkowski, proving experimentally the existence of an oxidizing substance, and is suggestive. Indeed, when, in addition to this, we realize the strength of Heidenhain's position, the manner in which it shook to its very foundation the equally strong position of Schiff's views as developed by Herzen, by pointing to *the influence of oxygen* as another agency through which trypsin could be developed from trypsinogen, "trypsin being oxidized trypsinogen," the following query suggests itself: Are we not dealing with two processes working in sequence, a part of the trypsinogen secreted in the splenic vein being converted by the splenic secretion for use in the portal vein, and the rest being converted, when the arteries are reached, by the oxidizing substance?

To determine whether such a deduction is at all warranted or whether it is subject to modifications through which the various views submitted and our own can be conciliated, we find it necessary to closely analyze the manner in which the pancreas and the spleen are functionally governed.

The Functional Mechanism of the Pancreas. — The pancreas will first receive our attention. Referring to this organ, Howell says: "Until recently little direct evidence had been obtained of the existence of secretory nerves. Stimulation of the medulla was known to increase the flow of pancreatic juice and to alter its composition as regards the organic constituents, but direct stimulation of the vagus and the sympathetic

nerves gave only negative results. Lately, however, Pawlow and some of his students have been able to overcome the technical difficulties in the way, and have given what seems to be perfectly satisfactory proof of the existence of distinct secretory fibers comparable in their nature to those described for the salivary glands. The results that they have obtained may be briefly stated as follows: Stimulation of either the vagus nerve or the sympathetic causes, after a considerable latent period, a marked flow of pancreatic secretion. The failure of other experimenters to get this result was due apparently *to the sensitiveness of the gland to variations in its blood-supply.*[12] Either direct or reflex vasoconstriction of the pancreas prevents the action of the secretory nerves upon it. Thus, stimulation of the sympathetic gives usually no effect upon the secretion, because vasoconstrictor fibers are stimulated at the same time; but if the sympathetic nerve is cut five or six days previously, so as to give the vasoconstrictor fibers time to degenerate, stimulation will cause, after a long latent period, a distinct secretion of the pancreatic juice. A similar result may be obtained from stimulating the undegenerated nerve if mechanical stimulation is substituted for the electrical. The long latent period elapsing between the time of stimulation and the effect upon the flow is not easily understood."

If the innervation of the stomach as we have interpreted it is recalled, Howell's lines furnish several confirmatory data. The fact that "stimulation of the medulla was known to increase the flow of pancreatic juice" suggests that our previous association of the vasomotor with the general motor system (sympathetic) was well founded. The vagus being, from our standpoint, the dominating nerve during pancreatic activity, as it is in the case of the stomach, it must also have been stimulated by its center at the proper time. Hence the secretion. That the vagus, as we have stated, assumes charge only during functional activity is further sustained by the statements that "stimulation of the sympathetic gives usually no effect upon the secretion" . . . "but if the sympathetic nerve is cut five or six days previously, so as to give the vaso-

[12] All italics are our own.

constrictor fibers time to degenerate" . . . "distinct secretion of juice occurs." Inasmuch as the sympathetic fibers are the vasoconstrictors, degeneration annulled their function (limited to *tonic* vasoconstriction), and the current caused reaction in the only normal nerves that remained, the vagi, which, as we have seen, inosculate with the sympathetic fibers around all vessels, and are the only ones capable of exciting physiological activity. Still, Pawlow obtained secretion by stimulating either nerve. The fact that "a considerable latent period" elapsed before the flow appeared suggests the reason for this; indeed—and it is very probable that earlier experimenters would also have obtained this result had they waited long enough—stimulation of either the vagus or the sympathetic was transmitted to the solar plexus, and, their own plexuses inosculating over the arteries, the state of functional activity was artificially brought on, though in a slow and deficient manner.

"The secretion is evidently reflex," says M. Duval, "though the nervous channels of this phenomenon are not exactly known; it has been noticed, however, that section of the pneumogastrics arrests the secretion of the pancreas." Conversely, "stimulation of the medulla is effective after section of both vagi," according to Foster. The solar plexus forming part of the general motor system (sympathetic), stimulation of the medulla is also transmitted to the pancreas, and the process defined in the last paragraph then prevails. That the blood alone may also sustain the organ's function is shown by the fact that when all its nerves are severed the secretion continues. But, initiated and governed by the vagus, this constitutes what might properly be termed a *pseudo-function.*

Referring to the blood-vessels, Piersol says: "The larger arterial branches run within the interlobular connective tissue, sending off vessels which pass between the lobules and supply the glandular parenchyma with twigs. These latter enter the lobules and form *net-works which inclose the individual acini within the capillary reticulum.* The capillaries lie beneath the basement membrane in close relation with the glandular epithelium. The veins accompany the arterial trunks within the connective tissue." A similar arrangement prevails in the

distribution of the nerve-terminals. According to Ramón y Cajal and C. Sala, the pancreas contains many nerve-cells and fibers of Remak. Some cells are found in the interacinous spaces; others are in contact with the intrinsic vascular walls, and *their finer prolongations surround the glandular cells.* Those connected with the vessels *form a plexus around them,* and send extremely fine filaments to the muscular elements. Alluding to the nerve-cells, Ramón y Cajal says: "We may consider this cell as a special cell, all the prolongations, or almost all the prolongations, of which possess the meaning of nervous prolongations *contrary to the cells of the sympathetic chain,* that have two kinds of prolongations: a long one, or fiber of Remak, for the viscera, and short prolongations comparable to the protoplasmic prolongations of cerebro-spinal cells, destined to establish relations by contact between the neighboring cells of a ganglion." Berdal, who quotes the above, therefore recognizes two varieties of nerve-fiber in the pancreas: "1. The nerve-fibers formed by the cellular prolongations and which supply the periacinous and perivascular plexuses. 2. The nerve-fibers derived from the sympathetic nerves which penetrate into the pancreas *with the vessels.* These nerves ramify between the lobules and contribute to the formation of the periacinous plexus." He then adds: "In the present state of the question it is impossible to say if the latter nerves terminate in a manner different from that of the former; and one cannot even indicate how they are related with the nerve-cells of the pancreas."

With our conception of the innervation of the stomach as guide, the relations between the two sets of nerves seem clear. That sympathetic and vagus branches are distributed to the organ, we have seen; it is evident that the fibers formed by the cellular prolongations are those of the vagus, since the others are recognized as sympathetic. The only path through which vagal fibers could enter the organ is, as in the case of the latter nerve, with the vessels. We have seen, when reviewing the mechanism of the stomach, that two-thirds of the fibers from the right vagus passed on to the solar plexus, and that extensions from the latter, also arranged "largely in plexuses," passed on "with the vessels" in company with the

sympathetic fibers. The pancreas forming part of this same system, the vascular as well as the nervous arrangement of the latter are undoubtedly similar. Indeed, we can repeat almost word for word the explanations given of the phenomena observed under the same conditions when the stomach was in question: *i.e., the general motor mechanism (sympathetic) serves only to maintain the tonic contraction of the vascular supply and the immanent potentiality of the pancreas when it is in the passive state, while the added impulses of the vagus excite and govern its functional activity.*

The functional mechanism of the pancreas would now be as follows:—

The nerve-supply of the pancreas is derived from two autonomous sources: the general motor system (sympathetic) and the vagus system.

The general motor system supplies efferent nerves, which only serve to maintain tonic contraction of the arteries and to insure the functional activity of all pancreatic structures during the passive or resting period.

The vagus system supplies both sensory and motor nerves, which excite and govern the functions of the pancreas during its active period.

The extrinsic efferent nerves of the pancreas, also derived from the "general motor" and vagus systems, accompany the organ's arterial supply and jointly constitute its extrinsic vasoconstrictor system: i.e., that through which the blood-flow in the organ is increased.

The intrinsic efferent nerves are divided into two sets: (1) branches of the general motor system; (2) branches of the vagus system.

(a) Each branch of the general motor system subdivides into two branches: one of these supplies the arterioles; the other subdivides into two branches, one of which is distributed to the muscles and the other to the glands.

(b) The branches of the vagus subdivide in the same manner and inosculate with the general motor filaments and plexuses except with those distributed to arterioles that supply capillaries to the glands.

When the pancreas is in the resting state, the general motor

nerves alone transmit impulses to all the structures of the organ, including the glands which, during this period, elaborate their secretory products.

When as a result of physical (reflex) or psychical stimuli the pancreas becomes functionally active, the vagus impulses impose their rhythm upon the general motor nerves, and the vagus system assumes control of the secretory process. As a result,

(a) The extrinsic arteries are constricted beyond their normal tonic caliber and the speed of the blood-flow through the organ is increased.

(b) The intrinsic arteries that do not supply capillaries to the glands are also constricted, thus forcing the blood into these capillaries and inducing glandular activity and the production of pancreatic secretions.

FUNCTIONAL MECHANISM OF THE SPLEEN.—The innervation of the spleen includes, as a predominating feature, the distribution of a fair proportion of the terminal fibers to the muscular elements, which, in man, are mainly supplied to the trabeculæ. "We have evidence," says Professor Foster, "that the muscular activity of the spleen, whether of the muscular capsule and trabeculæ and arteries combined, or of the latter alone, is under the dominion of the nervous system. *A rapid contraction* of the spleen may be brought about in a direct manner by stimulation of the *splanchnic or vagus nerves,*" . . . "it may also be caused by stimulation of the *medulla oblongata* with a galvanic current or by means of *asphyxia.* Though the matter has not yet been fully worked out, we have already sufficiently clear indications that the flow of blood through the spleen is, through the agency of the nervous system, varied to meet changing needs. At one time a small quantity of blood is passing through or is being held by the organ and the metabolic changes which it undergoes in the transit are comparatively slight. At another time a larger quantity of blood enters the organ and is let loose, so to speak, into the splenic pulp, there to undergo more profound changes, and afterward to be ejected by rhythmic contractions of the muscular trabeculæ."

That rapid contraction of the spleen should occur under stimulation of the splanchnic nerve is now easily accounted

for, when we recall the fact that, as shown by Biedl, Dreyer, and others, suprarenal activity is thereby enhanced, as shown by increased secretion. The marked muscular character of the spleen obviously causes it to respond by contraction to the increased amount of oxidizing substance suddenly thrown into the circulation, especially when we consider its direct connection with the cœliac axis. The constrictive effect of stimulation of the medulla on the arteries we have repeatedly seen; as this is due to contraction of their muscular coats, the spleen is evidently influenced in a manner similar to that following stimulation of the splanchnic. Again, therefore, have we as underlying cause of splenic contraction suprarenal overactivity.

But why should stimulation of the vagus also induce splenic contraction? This requires an examination of the distribution of the nerve-terminals. The innervation of the spleen was studied by Kölliker in various animals,[13] and his observations, when viewed in the light of our conceptions of the functional mechanism of glandular organs, are suggestive. "The vasomotor nerves enter the organ with the large arteries. In the *walls* of the large arteries the main trunks form a well-marked superficial *plexus* with oblong meshes in the adventitia, and a *deep*, more quadrate *net-work* in the tunica media; some end in the little branched arborizations in this coat. The smaller arteries and the trabeculæ receive their nerves from the rich maze of fibers in the pulp, consisting of axis-cylinders, which, however, do not anastomose. Other fibers form a plexus on the surface of the trabeculæ, and from this fibrils penetrate *into* the interior of the trabeculæ *(which contain much smooth muscle)* and end by free arborizations." Free terminals, which Kölliker regards as sensory fibers, were also found. When we consider that the trabeculæ penetrate deeply into the interior of the organ from the inner surface of the capsule in every direction, thus forming a spongy frame-work, it seems clear that stimulation of the nerves distributed to these structures and to the vascular walls should produce general contraction.

These data would not be sufficient to enable us to assimi-

[13] Kölliker: Sitzungsbericht d. Würsb. Phys. med. Gesellschaft, No. 2, 1893.

late the functional mechanism of the spleen to that of other organs reviewed were it not that *dilation* of the latter can also be produced by stimulating other nerves. Indeed, Howell says: "The spleen is richly supplied with nerve-fibers which, when stimulated either directly or reflexly, cause the organ to diminish in volume. According to Schäfer,[14] these fibers are contained in the splanchnic nerves, which carry also *inhibitory* fibers, whose stimulation produces a *dilation* of the spleen."

We have not so far found the need of such structures as "inhibitory nerves," and it would seem as if this term were applied, in this instance, to the fibers to which we have ascribed the mission of contracting the arterioles that govern the intrinsic blood-supply of an organ. Especially does this appear to be the case since these inhibitory fibers are described as originating from the splanchnic: *i.e.*, the sympathetic system. The latter, if considered as forming part of the general motor system, would precisely coincide with the origin of the nerves which have appeared to us to cause contraction of these small vessels and thus produce secondary dilation of the capillaries incident upon functional activity.

The interpretation of the splenic functional mechanism in accordance with our views is greatly facilitated when the microscopical anatomy of the organ is considered in the light of F. P. Mall's[15] researches. The organ is divided, as is the liver, into lobules, each of which is bounded by "interlobular" trabeculæ: those to which we have already referred. Each lobule is about 1 millimeter in diameter, is partitioned into about ten compartments by intralobular trabeculæ, and receives an artery which sends minute branches to each compartment. There is also considerable analogy between each one of these compartments and the hepatic lobule, the hepatic cells being represented by masses of pulp, separated by venules, which vessels carry back to the veins leading to the greater splenic vein the various elements transferred to the liver. The pulp itself is made up of an extremely delicate reticulum, in which are found red corpuscles, lymphocytes, remains of corpuscles

[14] Schäfer: "Proceedings of Royal Society," London, 1896, vol. lix, No. 365; and Journal of Physiology, 1896, vol. xx.

[15] F. P. Mall: Johns Hopkins Hospital Bulletin, Sept., Oct., 1898.

with or without pigment, etc. The arteries—which bring to the organ oxidizing substance—soon after entering the organ assume an unusual shape: their outer coat becomes lymphoid, forming nodules similar to the solitary follicles of the intestine,—*i.e.*, the Malpighian corpuscles,—in which lymphocytes are formed. When, after numerous subdivisions, their diameter becomes greatly reduced, the arteries resume their normal adventitia and on reaching the pulp in the compartments break up into minute capillaries. The arrangement is, after all, an uncomplicated one, and similar, in general plan, to that of other organs reviewed.

The connection between the nervous supply of the spleen and that of the other digestive organs becomes evident when the distribution of the cœliac-plexus branches is recalled. "The splenic plexus," say Pick and Howden,[16] "is formed by branches from the cœliac plexus, the left semilunar ganglia, and from the right pneumogastric nerve. It accompanies the splenic artery and its branches to the substance of the spleen, giving off, in its course, filaments to the pancreas (pancreatic plexus) and the left gastro-epiploic plexus, which accompanies the gastro-epiploica sinistra artery along the convex border of the stomach." If we append to this Kölliker's description of the intrinsic nervous supply and the manner in which it is connected with the blood-vessels, it will become apparent that we have a counterpart of the vasculo-nervous mechanism of the stomach, viz.: extensions of the general motor system (sympathetic) and of the vagus, the former being probably represented by the deep net-work in the tunica media, the latter by the oblong meshes of the adventitia. We have here the representatives of the extrinsic supply.

The functions of the Malpighian corpuscles around the vessels would thus be insured by fibers from the vagus. Indeed, Fusari[17] traced nervous filaments within these bodies. The pulp is also possessed of a "rich maze of fibers consisting of axis-cylinders"—doubtless sensory structures. But here an independent motor supply must also be present, since we also have fibers that form "a plexus on the surface of the trabec-

[16] Pick and Howden: "Gray's Anatomy," p. 806.

[17] Fusari: Archives Italiennes de Biologie, Turin, vol. xix, p. 288, 1894.

ulæ," filaments from which penetrate *into* the trabeculæ. These, we have seen, contain much smooth muscle, and the nerve-filaments are connected with them by "swellings" (Fusari), evidently end-plates. Kupffer's bile-alveolus, with its canaliculi, is recalled by a similar receptacle: *i.e.*, Mall's "intralobular venous spaces," which form the starting-point of the venules that ultimately end in the large trunks leading to the splenic vein.

If we now trace the process from beginning to end, the functional mechanism appears to us to be as follows:—

The nerve-supply of the spleen is derived from two autonomous sources: the general motor system (sympathetic) and the vagus system.

The general motor system supplies efferent nerves, which serve only to maintain tonic contraction of the arteries and of the trabecular muscles, thus sufficiently activating the flow of blood to the lobular compartments and to the Malpighian corpuscles to maintain their functional efficiency during the passive period.

The vagus system supplies both the sensory and motor nerves that excite and govern the functions of the organ during its active period, which begins about the fourth hour of digestion.

The extrinsic efferent nerves of the spleen, also derived from the general motor and vagus systems, accompany its arterial supply, and jointly constitute its extrinsic constrictor system: i.e., that through which the blood-flow in the organ is governed.

The intrinsic efferent nerves are divided into two sets: (1) branches of the general motor system; (2) branches of the vagus system.

(a) Each branch of the general motor system subdivides into two branches: one of these supplies the middle coat of the arteries and arterioles (the so-called inhibitory nerves); the other is distributed to the muscular elements of the trabeculæ.

(b) The branches of the vagus subdivide in the same manner: one branch supplies the adventitious layer of the arteries, sends offshoots to the Malpighian corpuscles, then passes on to the pulp, where it forms a close net-work; the other forms another plexus on the surface of the trabeculæ which inosculates with that of the pulp.

When the spleen is in the passive state, the general motor nerves alone transmit impulses to all the structures of the organ,

to sustain the continuous functional work of the lobular and corpuscular (Malpighian) elements (destruction of erythrocytes, formation of lymphocytes, formation of secretion, etc.) pending the active stage.

When, as a result of reflex stimuli through the efferent gastroduodenal branches of the vagus, the spleen becomes functionally active, the vagus impulses impose their rhythm upon the extrinsic motor plexuses (extensions of the splenic plexus), and the vagus system assumes control of splenic functions. As a result,

(a) The extrinsic arteries are constricted beyond their normal tonic caliber; the speed of the blood-flow into the organ is increased and the blood allowed to slowly accumulate therein (probably owing to restricted caliber of the venous exit), thus causing its dilation.

(b) About the fourth hour of the digestive process the arterial and venous calibers are equalized and the splenic products (secretion, leucocytes, broken-down corpuscles, and pigments) are voided into the splenic vein and increased rapidly. This continues for two to four hours, when the calibers are readjusted by the vagus and the organ resumes the passive state.

An incidental remark of Professor Mall's, in the contribution previously referred to, goes far toward demonstrating that we have not erred so far in ascribing to the blood-plasma *per se* the active part in the blood's function. This constitutes such a far-reaching feature of this entire work that the following lines appear to us as timely: "The microscopical anatomy shows that the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease and granules only with difficulty. In life *the plasma* constantly flows through the *intercellular spaces* of the pulp-cords, while the *blood-corpuscles keep within fixed channels.* Numerous physiological experiments which I have made corroborate this view." If this can occur in the spleen it is doubtless possible elsewhere in the organism, especially when we consider that red corpuscles average in diameter about $^{1}/_{3000}$ of an inch, while the lumen of the majority of functional capillaries is less than one-half that size. Of course, corpuscles adjust themselves to the dimensions of the structures surrounding them; but it is apparent that in many instances—the tortuous capillaries of pericellular net-works, for instance—such a system

could but compromise the free circulation of the fluids, and, simultaneously, the functional efficiency of the organ itself.

THE SPLENO-PANCREATIC INTERNAL SECRETION.—Resuming the consideration of the relationship between the functions of the two organs, spleen and pancreas, it is evident that each possesses its own complete mechanism, and that *in both organs, as elsewhere in the economy, the oxidizing substance or the blood containing it is the source of functional activity.*

Still, have we any reason to believe, with Popelski, that it is through oxidation that the intrapancreatic trypsinogen becomes converted into trypsin? Can we say, for instance: the intrapancreatic conversion of trypsinogen into trypsin is not effected by the splenic ferment, but by the oxidizing substance, when the efferent vagus nerves transmit appropriate impulses? We think not, much as such a process would coincide with the multiple functions that we have already ascribed to the oxidizing substance.

We have seen that when the pancreas becomes functionally active the extrinsic arteries are constricted beyond their tonic caliber, and that the speed of the blood-flow through the organ is increased. Yet, while the net-work of capillaries is very rich, these *encircle* the secreting lobules, and, though in close relation with the glandular epithelium beneath the basement membrane, they in no way, as in the spleen, break up into reticulated tissue wherein their blood is poured; they merely lapse, as elsewhere in the organism, into venules, which ultimately carry the blood to the larger venous channels. Blood and trypsinogen do not come into contact, therefore, in the ducts of the typical pancreatic lobule: that which textbooks employ to illustrate the origin, centripetal migration, and functional elimination of the zymogen granules. These are lost in the lobular lumina and ultimately reach the greater duct on its way to the intestine, without apparently having come into contact with the oxidizing substance.

But, this being the case, how can we account for the experimental evidence adduced by Schiff and Herzen and other physiologists who have confirmed their work? How can we explain, for instance, the digestion of 17 grammes of albumin in 7 hours with pancreas obtained from a normal cat and *no*

digestion in 12 hours with pancreas from one in which the vessels of the splenic hilum had been ligated: an experiment repeated many times, and always with identical results?

It is evident that, if—as believed by Schiff and Herzen—the circulatory cycle must be traversed by the splenic ferment before the pancreas can be influenced by it, this ferment will merely pass *through* the pancreas without in any way converting trypsinogen into trypsin, and fruitlessly re-enter the splenic venous current. There being no connection between blood-stream and trypsinogen and none between the latter and the splenic ferment, we are now reduced to either deny the need of any converting agency, and simultaneously close our eyes to all the experimental data adduced,—including Popelski's, which sustain the existence of *some* process which has imposed the necessity upon him of accounting for *results* witnessed,—or seek elsewhere for an explanation of the phenomena recorded. Thanks especially to the labors of Langerhans,[18] Laguesse,[19] and Opie,[20] this task will be greatly facilitated.

Laguesse having studied the islands of Langerhans in the pancreas of an adult man (an executed criminal) and of a child which had died several hours after birth without having taken nourishment, and in the sheep, reached the following deduction, quoted from one of our own reviews of his work[21]: "Long before the pancreas begins its function as a digestive gland granules of secretion accumulate in the internal zones of the cells; and, when these come *into contact with the blood*, a portion of them appear as though dissolved, while in others the granules are resorbed. It might be supposed, with some reservations, that an internal secretion always exists in the cell,—very much developed, however, and preceding the external secretion in the fœtus. Later, each cellular group would be first full, then acinous, furnishing alternately an internal and an external secretion." Opie refers to the observations of Kühne and Lea[22] in injected specimens, in which these in-

[18] Langerhans: Inaugural Dissertation, Berlin, 1869.

[19] Laguesse: Comptes-Rendus Hebdom. des séances et mémoires de la Société de biologie, Paris, No. 28, 1893.

[20] Opie: Johns Hopkins Hospital Bulletin, Sept., 1900.

[21] Laguesse: "Annual of the Universal Medical Sciences," vol. v, 1894.

[22] Kühne and Lea: Untersuch. a. d. Physiol. Inst. d. Univ. Heidelberg, ii, 488, 1882.

vestigators "found scattered through the organ glomerular structures composed of dilated and tortuous capillaries, and showed that these glomeruli correspond to the cell-groups which Langerhans described. The islands are penetrated by numerous wide, tortuous capillaries, which lie between cells, forming irregular, anastomosing columns. Material injected into the *duct* of the gland does not penetrate the islands." The view that the islands of Langerhans furnish an internal secretion is indirectly sustained, and the histological topography outlined seems to furnish a clue to the mechanism involved: *i.e., the existence of two sets of glands capable of yielding similar products, but adjusted individually, as regards distribution, to the needs of two systems: the digestive system and the circulatory system.*

To develop this proposition and that on page 379, we will employ the excellent paper of E. L. Opie,[23] in which the entire subject is not only reviewed, but also greatly elucidated through personal investigations. The quotations from his article will be limited, however, to the features bearing directly or indirectly upon the question in point, as given in the above italicized lines:—

"Schäfer and Diamare think that the vascular islets probably furnish an internal secretion. The only evidence in support of this suggestion is contained in the short preliminary notice of Ssobolew. He states that after feeding animals on carbohydrates the cells of the islands become more granular. After ligating the duct of Wirsung in dogs, the islands of Langerhans, he finds, are not involved in the sclerotic process which follows. He thinks that this fact explains the absence of glycosuria after ligation of the pancreatic ducts. In human cases I had observed after duct obstruction similar resistance of the islands to the consequent inflammation. In pancreases of two diabetics Ssobolew was unable to discover islands of Langerhans.

"In the human pancreas the islands were found to be more numerous in the splenic end, or tail, than elsewhere. To obtain a numerical statement of their relative abundance, their

[23] E. L. Opie: *Loc. cit.*

number was determined in a sectional area of 0.5 square centimeter. Sections about 10 millimeters thick were made from the enlarged duodenal portion of the pancreas, or the head; from the midportion, or body; and from the splenic end, or tail. The following table gives their number in an area of 0.5 square centimeter in sections taken from the head, body, and tail of ten normal organs:—

TABLE I.

	HEAD.	BODY.	TAIL.
I	11.0	13.0	30.0
II	30.0	25.0	42.0
III	4.0	4.0	19.0
IV	4.0	10.0	13.0
V	27.0	18.0	59.0
VI	25.0	27.0	26.0
VII	18.0	18.0	29.0
VIII	6.0	10.0	29.0
IX	44.0	32.0	61.0
X	14.0	23.0	32.0
Average	18.3	18.0	34.0

"The table shows that the islands are more abundant in the tail, or splenic end, than in the head and in the body, where they are present in approximately equal number. They are almost twice as numerous in sections from the tail as in those from other parts. Since the number in only one plane is recorded, in order to obtain their actual relative abundance it is necessary to square these figures. They are then found to be slightly less than three and a half times as numerous in the tail as elsewhere.

. . . . . .

"The cells composing the islands resemble those of the acini. They have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body. The basal zone of the secreting cell, as is well known, stains deeply with nuclear dyes,—for example, hæmatoxylin or methylene blue,—while the central portion, which contains zymogen granules, remains unstained. The cells of the island, however, do not stain with nuclear dyes, while with eosin their protoplasm takes a homogeneous bright-pink color. The nuclei differ but little from

those of neighboring acini. They vary considerably in size, and not infrequently one finds very large round vesicular nuclei whose diameter is two or more times that of those about. Occasionally the cells, forming columns between which are the anastomosing capillaries, are very closely packed together, and nuclei are situated almost side by side; more frequently the cells of the island are less numerous and the nuclei are less closely crowded together.

"The outline of the island is usually round or oval, and is not infrequently accentuated by a delicate circle of fibrous tissue. In other instances the outline is less sharp, and the body accommodates its shape to that of the neighboring acini. Occasionally one sees, apparently within the island, cells arranged, as in the acini, about a central lumen, and, indeed, in many instances it is difficult to convince one's self that they do not form part of it. The impression is produced that the columns of the island are in continuity with cells having an acinar arrangement. Since the islands and the secreting acini have a common origin, it is not inconceivable that they may occasionally remain continuous in the adult organ. When the fœtal pancreas is affected by congenital syphilis, the islands, I have found, retain their continuity with the secreting structures.

"In the human pancreas the groups of acini about terminal ducts are not sharply defined by connective tissue; so that individual lobules, as in the human liver, are indistinctly marked off and in places apparently fuse with one another. In the pancreas of the cat the lobules, like those in the liver of the pig, are much more sharply outlined by interstitial tissue. Details of structure have been studied in the pancreas of the cat.

"The parenchyma is divided by septa of fibrous tissue into small polygonal areas in size and shape. When injected with Berlin blue, a small ramification of the ducts is found to penetrate the isolated group of acini. These subdivisions, or lobules, often appear completely isolated by fibrous tissue from those near by, but when one of them is traced through a series of sections its separation may be uniform, and in places one finds the parenchyma of adjacent lobules in contact, the

dividing septa being incomplete. That these polygonal structures are actually independent of one another and represent units of structure is readily demonstrated by causing an inflammatory increase of the interstitial tissue. If the pancreatic ducts of a cat are ligated and the animal killed at the end of two or three weeks, the gland is found to be the seat of a chronic interstitial inflammation, characterized by an increase of the interlobular tissue. The lobules are completely separated from one another by narrow bands of firm, fibrous tissue, and occur in sections as rounded, triangular, or polygonal areas of parenchyma.

"The islands of Langerhans occupy a position near the center of the lobule, and in the splenic end of the gland each lobule contains an island. In a given section many lobules whose limits are more or less distinctly outlined are seen to contain islands situated near their center, while in neighboring lobules such structures may not be discoverable. If, however, serial sections are studied, every lobule is found to contain an island. Its presence within the lobule is not constant in other parts of the organ, and in the extremity of the descending arm of the gland they are very few in number.

"The lobules are grouped about the medium-sized ducts. The main ducts give off branches approximately at right angles to their course. Branching one or more times, a duct forms the center of a group of lobules, which is usually elongated in form and tapers to a point at or near the surface of the gland. Such lobule groups are separated from one another by relatively wide bands of areolar tissue much looser in texture than that separating the individual lobules. The lobule groups in the fresh state or in tissue macerated a few days in Muller's fluid may be separated from one another by careful teasing. In the loose tissue lie the larger ducts, arteries, veins, and nerves. An artery and vein penetrate each lobule group in company with the duct, and ramify between its lobules. The smallest arteries occasionally penetrate the lobules, but usually branches, diminishing in size, give off capillaries which enter the lobule and form a close net-work between the gland-acini.

"The capillaries of the island of Langerhans form a

glomerulus of tortuous, freely-anastomosing vessels, much thicker than those between the acini. A single afferent vessel like that of the glomerulus of the kidney does not enter this group of dilated capillaries, but numerous anastomoses make it continuous with the interacinar capillaries. When Berlin blue is injected through the aorta into the arteries of the pancreas, it not infrequently happens that in portions of the gland which are poorly injected the vessels of the island

CAMERA-LUCIDA TRACING OF THE LOBULE BOUNDARIES IN ONE OF A SERIES OF SECTIONS FROM THE SPLENIC END OF A CAT'S PANCREAS.

The majority of the lobules are well defined. Those marked *d*, *e*, *f*, *g*, and *h* are poorly outlined, but are found to be more readily distinguishable when traced through the series of secretions. The lobules, which are lettered (*a* to *o*), were traced through the series, and each was found to contain an island of Langerhans situated near its center. The section passes through the island in lobules *a*, *e*, *i*, *j*, and *n*. (*Eugene L. Opie.*)

are filled with the injected mass, while the surrounding capillaries are, for the most part, empty. If instead of soluble Berlin blue a granular injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the interacinar capillaries contain little of the injected material. The glomerular net-work is in very free communication with the smallest arteries, and apparently has a richer blood-supply than other parts of the lobule.

"In the human pancreas lobules and lobule groups are not so regularly arranged as in the cat. But both structures are more or less clearly definable. The lobules vary much in size, and are usually not clearly separated from one another. Though an island of Langerhans is often situated in the center of a more or less clearly defined lobule, no constancy of position is discoverable. The lobule groups are separated by relatively wide bands of loose areolar tissue in which are contained the medium-sized ducts, the blood-vessels, and the nerves. Within a lobule group the arteries and veins, which are side by side, do not, as in the cat, accompany the ducts."

The multiplicity of facts reviewed in the foregoing pages and the intricacy of the whole question make it necessary to collate and group in logical sequence the salient features of each subject discussed, in order to render a fruitful comparison of their merits possible. Not only are we required to analyze the questions involved in the light of the solid data that the last forty years have furnished,—*i.e.*, since Schiff first studied the relations between the spleen and the pancreas,—but all these must likewise be sustained by, and be in accord with, the functional mechanisms of the organs involved as we interpret them, if our own views are well founded. If they are, they must necessarily assist us greatly in elucidating the various problems, physiological and pathological, to which reference has been made, since the very elements which they introduce bear upon a predominating factor in all these processes: *i.e.*, oxidation. To this subdivision of the subject we will, therefore, turn our attention.

Can we ascribe to oxygen, or rather to the oxidizing substance of the blood, the conversion of pancreatic trypsinogen into trypsin? We have seen that in both the spleen and pancreas the oxidizing substance seems, as elsewhere, to play the main functional rôle; the extrinsic and intrinsic vessels are disposed in a similar manner as regards their nervous relations, and vasoconstriction calculated to increase the flow of blood through both organs is similar. Moreover, we have seen that in the spleen the dilation incident upon malarial intoxication could be traced to the adrenals,—the primary source of excessive oxidation,—while in toxic glycosuria we obtained

as clear evidence that overactivity of the pancreas could also be ascribed to these organs. Again, the ease with which oxygen is thought to convert trypsinogen into trypsin—a mere current of oxygen through a solution of zymogen sufficing to produce trypsin—has been fully emphasized. Besides Heidenhain's labors in this connection, we need but recall Schiff's experiment with the two halves of a pancreas, one of which was infused at once and the other left exposed to the air a day, with the result that the latter alone proved active; and also that of Herzen, in which an infusion of active spleen mixed with an infusion of inactive (hence zymogen-laden) pancreas proved very active, while a pancreatic infusion mixed with one of inactive spleen digested nothing. Heidenhain ascribed to oxidation the conversion into trypsin, in this experiment. Indeed, when we consider the wealth of oxygen in the blood supplied the pancreas, direct from the lungs via the cœliac axis, it would seem as if it should be the predominating factor of the conversion processes involved.

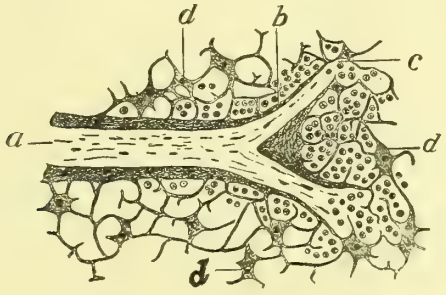
And yet, the oxidizing substance being a constituent of the blood-plasma, it would have to penetrate into the ducts *per se* and *as* oxidizing substance in order to carry out the required reaction. There is no evidence that a direct channel, such as there is in the spleen, by means of which the capillaries directly pour their blood into the secreting structures, exists. As may be seen in the annexed illustration, the splenic vessels actually terminate in the latter; "their walls become much attenuated, lose their tubular character, and the cells of the lymphoid tissue of which they are composed become altered, presenting a branched appearance and acquiring processes which are directly connected with the processes of the sustentacular cells of the pulp."[24]

Nor is there evidence that canaliculi such as those of the hepatic cell exist by means of which the blood-plasma or its contents may directly find their way to a structure corresponding to bile-channels, which in the pancreas would be represented by the ducts. Langerhans long ago demonstrated that canaliculi were present in the lobules between the epithelial

[24] Pickering Pick and Howden: "Gray's Anatomy," 1901.

cells, but these, besides being pyriform, terminate as blind pouches, with their orifice directed toward the glandular lumen. Saviotti also found these minute, delicate, pouch-like channels. Ramón y Cajal, using the Golgi method, found that they sent offshoots into the cells themselves, but that these also ended as blind pouches, their ampullar dilations never reaching beyond the line which separates the granular portion of the cell from the clear area. It is evident that these constitute collecting channels for the products of glandular metabolism: a further indication that no free channel between the blood-stream and the ducts exists.

Indeed, experimental proof to this effect is available: When the histological examinations of Kühne and Opie were



TERMINATION OF SMALL BLOOD-VESSELS IN THE SPLEEN. (*Gray.*)

a, Small artery. *b*, Vessel undergoing lymphoid change. *c*, Vessel continuous with supporting cells. *d*, Supporting cells.

mentioned on page 394, it was noted that material injected into the *duct* of the gland did not penetrate the islands of Langerhans. If, on the other hand, Opie's observation that injections of Berlin blue often filled the vessels of the island *per se*, leaving the majority of surrounding capillaries empty, is considered in this connection, it is evident that there can be no direct communication between ducts and blood-stream through either the islands of Langerhans or the glandular lobules that contain them. This involves an all-important deduction, however, viz.: that the splenic ferment, as well as the oxidizing substance, merely passes through the pancreas in transit, the latter, in its usual capacity of reagent, being intended only to activate function.

But how, under these circumstances, can we account for the experimental results reached by Schiff and Herzen, Heidenhain, Lépine, Pachon and Gachet, and Popelski? All these observers in one way or another have unquestionably shown a direct relationship between the blood-serum and trypsinogen, Heidenhain and Popelski considering oxygen as the converting agency, with solid experimental data to sustain them; Schiff, Herzen, and the other investigators mentioned attributing to the splenic ferment the same mission, with equally strong experimental backing. How account, for example, for the results observed in the following experiment of Herzen's? Two fasting dogs, having received all the meat they could eat, were at once submitted to ligation of the pylorus, bile-duct, and jejunal end of the duodenum, and also, in one of the dogs, of the hilum of the spleen. Albumin having been introduced into the duodenum, both dogs were killed after seven hours. In the dog with ligated splenic hilum the albumin was intact; in that in which the splenic vessels were free, the albumin had disappeared. This and other experiments to which we have referred may, indeed, be said to prove—whichever be the prevailing converting agency—that a communication between the blood-channels and the ducts exists.

We have seen that there is no evidence to show that the acini in direct communication with the ducts also open into the blood-vessels; these, as elsewhere, form a close net-work around the acini, but they do not open into the blind pouches of the latter. Could the communicating channels traverse the islands of Langerhans? That these organs do not possess such channels or even ducts has been shown by Dogiel,[25] who studied this question in a well-preserved human pancreas treated by the chrome-silver method, and in which the gland-ducts, "even in their finest intra-alveolar branches, were well stained." Yet these structures possess morphological characteristics that are suggestive. Dogiel, for example, found that they possessed relatively large capillaries located in the cellular trabeculæ. All investigators seem to agree upon the unusual size of those vessels. Kühne and Lea define the islands as "glomerular

[25] Dogiel: Böhm and von Davidoff, *loc. cit.*

structures composed of *dilated* and tortuous capillaries." Opie calls them "vascular islets" which are in "very free communication with the smallest arteries and apparently have a richer blood-supply than other parts of the lobule." That these dilated arteries are possessed of special functions is suggested by the fact that, "if, instead of a solution of Berlin blue, *a granular* injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the intra-acinar capillaries contain little of the injected material." They appear to constitute alveoli or ampullæ rather than true vascular channels, in which what blood passes through them is submitted to some kind of process.

An interesting feature in this connection was noted by Opie, viz.: the fact that the cells of the islands of Langerhans are in some instances continuous with the regular glandular elements of the organ, in such a manner as to prolong the ducts of the latter by encircling them. "Occasionally," says the author, "one sees, apparently within the islands, cells arranged, as in the acini, about a central lumen, and, indeed, in many instances, it is difficult to convince one's self that they do not form part of it." This intimate relationship between the two sets of glandular elements is further emphasized by the manner in which their capillaries are related. While the smaller arteries or arterioles ramify between the lobules and supply the net-work of capillaries to the acini, they also communicate with the tortuous and dilated vessels of the islands of Langerhans; so that the latter, as regards their vascular relations, really constitute glomerular expansions and offshoots of the regular acini's blood-channels. We thus have two sets of superposed glands around a common duct, the upper, or common acini, pouring their own secretion (or granules) into it through their microscopical ducts; the lower, those of the islands—possessed of no ducts or other orifices—presenting their dilated capillaries or alveolar walls so as to cause them to face, and perhaps slightly project into its lumen. If we now replace by an active circulation through all these vessels the cinnabar or ultramarine-blue injections referred to above, the accumulation of the latter in the islands distinctly points to a similar process during life: *i.e.*, accumulation of blood and

its normal result (with narrower blood-vessels at each end of the glomerulus): *i.e.*, centrifugal pressure.

If we now conjoin Opie's remark—"the impression is produced that the columns of the island are in continuity with cells having an acinar arrangement"—and Mall's observation, in his study of the microscopical anatomy of the spleen,—that "the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease . . ."—it seems probable that we hold the key to the situation. Indeed, what have we in the dilated glomerules of capillaries of the islands of Langerhans but vascular ampullæ? Centrifugal pressure under the circulatory conditions mentioned can have but one result: *i.e., filtration of the blood-fluids through the ampullar walls and into the ducts.*

It is, perhaps, unnecessary to point to the fact that, besides being the only functional mechanism warranted by the anatomical structures present, it also meets all the requirements of the well-founded experimental data adduced. The precision with which it seems to harmonize the two seemingly antagonistic features of the general function represented—*i.e.*, the Schiff-Herzen spleno-pancreatic process and the Heidenhain zymogen-oxidation process—is also noticeable. If we also realize that all these elements of the general function now fall sequentially in the normal order of their physiological usefulness, it will become apparent that we must have reached a solution worthy of confidence. This may be formulated as follows:—

1. The splenic ferment secreted into the splenic vein is carried to the portal vein through the liver, thence by the hepatic vein to the inferior vena cava, and after passing through the cardio-pulmonary circuit is distributed throughout the entire organism.

2. The quantity of splenic ferment distributed to the pancreas is proportionate to the amount of blood carried thereto by the pancreatic subdivisions of the splenic artery, and represents but a fraction of that supplied to the general circulation.

3. The splenic ferment distributed to the pancreas follows the course of its blood-channels, and is distributed to the cellular elements of the organ dissolved in the blood-plasma.

4. On reaching the cellular elements, the plasma, through its

oxidizing substance, insures functional metabolism of both glandular structures present,—the lobular acini and their immanent structures, the islands of Langerhans,—which metabolism, during the passive, or inactive, state of the organ, ends in the formation of the secretion granules.

5. When at the end of the fourth hour of general digestion the pancreatic ferments are required in the intestinal canal, the vagus incites, sustains, and governs the functional activity of both the pancreas and the spleen, and thus insures their synchronous action as long as the pancreatic ferments are needed.

6. Intrinsic-nerve constriction of the arterioles that supply both the pancreatic lobules and the islands of Langerhans with capillaries constitutes, as elsewhere, the mechanism through which glandular activity is sustained; but, the islands' vascular ampullæ possessing no muscular layer, they become the seat, owing to their large size, of sufficient blood-pressure to cause the blood-plasma and its contained splenic ferment and oxidizing substance to filtrate through their walls.

7. Some lobules are entirely composed of true secreting cells; others contain, besides, islands of Langerhans. In the latter lobules the secretion, therefore, consists of two different bodies: the granules of the true secreting cells and the blood-plasma derived by filtration from the islands.

8. The true secreting cells and those of the island being in continuity and surrounding a common lumen (Opie), both bodies —(1) the zymogen, or trypsinogen-forming, granules, and (2) the plasma containing the splenic ferment and the oxidizing substance —meet in this common lumen, which connects with the terminal ramifications of the pancreatic duct.

This is about as far as we can proceed at present, since we can only surmise that, as soon as the products referred to meet in the glandular lumen, the splenic ferment at once converts the trypsinogen granules into liquid trypsin. Interesting in this connection, however, is the fact, observed by Laguesse, that "long before the pancreas begins its function as a digestive gland granules accumulate in the internal zones of the cells; and when these come into contact with the blood a portion of them appears as though dissolved." As is well known, this is precisely what happens even in true acini that do not belong to

lobules supplied with islands. When secretory activity occurs, the granules of the inner zone of the cells simply disappear in the central lumen; but how and in virtue of what agency they are transformed into secretion at this point has not been determined. In the lobules supplied with islands of Langerhans the effused serum more than satisfies this feature, since it supplies two agencies thought to be capable of converting the granules into trypsin; but what of the lobules deprived of islands? How are *their* granules converted?

To answer these questions we must first ascertain which of the ferments credited to the pancreas can be shown to originate in the true acini. We have seen that, when the hilum of the spleen is ligated and no splenic ferment can find its way to the blood, the digestion of albumin ceases. It is, therefore, evident that, in accordance with Herzen's view, the splenic ferment is a *sine qua non* in the process through which trypsinogen is converted into trypsin. But why does the oxidizing substance not continue the conversion after ligation of the splenic hilum? There is but one answer to this, viz.: *zymogen and trypsinogen are not similar bodies; while zymogen is converted into some pancreatic ferment by oxygen, trypsinogen is not, and always requires the splenic ferment.*

To illustrate this fact we submit, *in extenso*, two of Gachet and Pachon's experiments, performed to show that it was the spleen's ferment, and not its hæmoglobin, that converted protrypsin, which they term "proferment." Believing that zymogen, which, as shown by Heidenhain, is very greedy for oxygen, and "proferment" are the same bodies, their aim is to prove that, injected in arterial blood, pancreatic ferments cannot be converted into trypsin therein. But, interpreted from our standpoint,—since the blood contains oxidizing substance which zymogen would readily take up,—these experiments prove that zymogen and their proferment (trypsinogen) differ, as stated.

"As the proferment of the pancreas becomes very easily transformed into trypsin under the influence of oxygen," say Gachet and Pachon, "it seems possible that splenic extracts, intensely colored by the hæmoglobin, should owe their trypsinogenous power to the fixed oxygen of hæmoglobin which

they hold in solution. If such is the case, arterial blood, richer in oxygen, should render a pancreatic infusion containing the proferment more active than venous blood. A. Herzen has already studied this question and antagonized it by means of appropriate experiments. On our side, we have tried to ascertain the value of this opinion in the following manner:—

"*Experiment II.*—The pancreas of a fasting dog was allowed to macerate two hours in ten times its volume of a saturated solution of boric acid. By decantation, 200 cubic centimeters of the maceration liquid were taken and distributed among four flasks: A, B, C, and D.

"To A were added 20 cubic centimeters of defibrinated *arterial* blood (obtained from the fasting dog).

"To B were added 20 cubic centimeters of defibrinated venous blood (obtained from the fasting dog).

"To C were added 20 cubic centimeters of *congested* spleen (aqueous maceration).

"To D were added 20 cubic centimeters of distilled water.

"These flasks, in each of which was introduced 1 cubic centimeter of albumin, were then placed in the oven at 39° C.

"At the end of 4 hours beginning digestion was observed in flask C; villosities appeared on the surface of the cube of albumin, which continued to be attacked in an energetic manner.

"A and B, after remaining in the oven 24 hours, did not show very clear traces of digestion. Their cubes of albumin presented slightly less sharp projections, and their angles were more rounded. The cube in flask D was slightly attacked.

"*Experiment III.* — The pancreas of a fasting dog was divided into three parts and triturated: the first alone; the second with 20 cubic centimeters of femoral arterial blood; the third with 20 cubic centimeters of venous blood, taken, as was the former, from a fasting dog. These were placed in flasks A, B, and C, containing each 150 cubic centimeters of boric-acid solution. After remaining 2 hours in the oven the peptonizing power of the decantation liquids was tried. Their proteolytic action was very slow; the first signs of digestion had appeared: in A after 16 hours of oven; in B and C after 20 hours. Digestion was not further advanced in the flask

containing arterial blood than it was in that containing venous blood.

"It can be seen that in these two experiments arterial blood showed itself as inactive as venous blood. One cannot, therefore, ascribe the unquestionable action of the extract of congested spleen upon the pancreatic proferment to the oxygen of splenic tissue."

There is one feature in this connection, however, which requires elucidation: the influence that the use of *fasting* dogs might have had on the experiments. We have seen that under these conditions suprarenal activity becomes reduced; the blood may, therefore, contain but a minimum of oxidizing substance. Herzen performed an experiment which not only confirms our conclusion that zymogen and trypsinogen are not identical bodies, but also shows that fasting does not influence the results just given. As Herzen's experiment has already been reviewed at length, we will only reproduce its salient points. The pancreas of a fasting dog (hence rich in trypsinogen and other ferment-forming agencies) was infused in glycerin, and this in turn was mixed with eight samples of blood (bled directly in double its quantity of glycerin), four being taken from a fasting dog and four from a dog in full digestion with its spleen greatly dilated. The four samples were taken in both animals from the femoral artery, the femoral vein, the splenic artery, and the splenic vein. Fibrin was then added to each sample. "After 1 hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic *venous* blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the *digesting* dog; the fibrin had almost entirely disappeared under the influence of the *splenic venous* blood of the same animal." This seems to us to confirm not only the view held by Herzen, that the splenic ferment is the only agency capable of converting trypsinogen into trypsin, but also that trypsinogen does not, like zymogen, possess affinity for oxygen.

This may be further demonstrated by showing that oxygen does exist in the blood, and that if we were dealing with zymogen it would be oxidized therein. The oxidation of sugar converted from glycogen, we have seen, represents the main factor in the production of functional energy in the muscles and other structures. That sugar occurs in the blood normally, but in small quantities, its combustion therein depending mainly—as in toxic glycosurias—upon suprarenal activity, we have also seen. The more these organs produce of their secretion, the greater is the proportion of oxidizing substance in the blood, and suprarenal insufficiency means a corresponding increase of sugar in the blood through imperfect oxidation. Hence the oxidizing substance is a sugar-destroying agency.

That an agent capable of consuming sugar exists in the blood was ascertained by Lépine in 1889, who named it "glycolytic enzyme." Howell, referring to this substance, says: "It has been asserted by Lépine and Barral that there is normally present in the blood an enzyme capable of destroying sugar. Their theory rests upon the *undoubted fact that sugar added to blood outside the body soon disappears.*" This obviously constitutes another proof of the existence of oxidizing substance in the blood.

Howell, referring also to the supposed source of Lépine's glycolytic enzyme, says, referring to the pathogenesis of glycosuria: "The most plausible theory suggested is that the internal secretion produced contains a special enzyme, glycolytic enzyme, whose presence in the blood is necessary for the consumption of sugar. Such an enzyme *may be obtained from the blood*, but it is not proved whether it is a normal constituent or whether it is produced after the blood is shed by the disintegration of some of its corpuscular elements." . . . "It is interesting and suggestive to state, in this connection, that post-mortem examination in cases of diabetes mellitus in the human being has shown that this disease is associated in some instances with obvious alterations in the structure of the pancreas." That the glycolytic enzyme is, as oxidizing substance, a normal constituent of the blood is obvious; but the interesting feature to determine now is whether, as believed by Lépine, the pancreas is the source of the ferment, since, if it

were, it would constitute an additional factor in this organ's physiological functions.

To which of the two pancreatic active structures can we hypothetically ascribe the formation of the glycolytic enzyme? Laguesse[26] has ascribed this function to the islands of Langerhans. That these structures underlie some physiological process in addition to that already analyzed by us is undoubted. The fact that they contain large nuclei shows that they are physiologically active. "The cells composing the islands resemble those of the acini," says Opie; "they have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body." They must produce some ferment or its zymogen, for Ssobolew found that feeding animals on carbohydrates caused them—*i.e.*, their protoplasm—to become granular. This is indirectly confirmed by the fact that these bodies are often found diseased in diabetes. They had entirely disappeared in two of Ssobolew's cases. In a case of Opie's[27] hyaline metamorphosis was strictly limited to the islands of Langerhans, the glandular acini remaining intact. Flexner[28] refers to this cause of diabetes as follows: "That it depends upon an internal secretion supplied by the pancreas to the blood is highly probable. Whether this hypothetical secretion is the product of the cells of the islands of Langerhans is unproven."

The data bearing upon this source of diabetes are very few,—an unfortunate fact, since these particular structures seem to us to play the predominating rôle in the production of glycosurias of pancreatic origin, now that we have ascertained that they are, through their ampullæ, the only thoroughfares for the splenic ferment. Still, can we, with Laguesse, now consider them as the source of a glycolytic ferment? Were we to admit this possibility, we would find ourselves obliged to concede that the pancreas supplies the intestinal tract with a glycolytic ferment besides an amylolytic ferment, and we would have, as a result, the formation of maltose from food-starches and its immediate destruction by the glycolytic fer-

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[26] Laguesse: *Loc. cit.*

[27] Opie: Journal of Experimental Medicine, March 25, 1901.

[28] Flexner: University of Pennsylvania Medical Bulletin, Jan., 1902.

ment, thus annulling the very important functions of sugar in the economy.

It is plain that the islands of Langerhans are not the source of a glycolytic ferment. Of course, Professor Lépine has never, that we know of, sustained this view, his contention being simply that the normal pancreas contains a glycolytic ferment which finds its way into the lymph and blood, in which it controls the consumption of sugar by the tissues. And his experimental evidence, in the light of our views, shows this to be the case, since it all goes to prove that the oxidizing substance which enters the pancreatic circulation is a glycolytic body. This does not mean that it acts therein as such; indeed, the organic cells at once take up its oxygen for their own functional interchanges, the blood returning to the splenic veins as venous blood. But it is nevertheless obvious that Lépine should have experimentally found, as he says, a glycolytic ferment in the pancreatic blood. All we show, therefore, is that *Lépine's glycolytic ferment is the oxidizing substance.*

But why should disease of the pancreas under these circumstances increase the proportion of sugar in the urine: a feature which Lépine ascribed to decrease of sugar destruction and to the fact that "these lesions decrease the source of the glycolytic ferment in the economy"? From our standpoint, of course, the adrenals are the original source of the oxidizing substance: *i.e.,* adrenal secretion *plus* oxygen. But does this account in an equally satisfactory manner for glycosuria? This introduces a very important feature of the entire analysis, one, indeed, bearing upon the pathogenesis of all forms of pancreatic diabetes.

We have previously referred to the fact that disease of the islands of Langerhans had been found to be a prominent causative factor of diabetes by various pathologists, and that Opie had witnessed a case in which these islands *alone* were diseased. This obviously points to the fact that, *if in accordance with our view the ampullæ of the islands are the pathways of the Schiff-Herzen splenic substance to the ducts,* we are dealing either with obstruction or impaired conversion of trypsinogen into trypsin, or both simultaneously. If, bearing this feature in mind, we review the list of pancreatic diseases that cause

glycosuria, it will become apparent that these two factors account for the phenomena observed in many cases: calculi, lipomatosis, hypertrophy, tumors, induration, and periglandular sclerosis. Atrophy,—a condition which in itself implies functional impairment,—on the other hand, constitutes the majority of the remaining pathological processes encountered post-mortem in this organ.

But the question which now imposes itself is this: Why and how does a condition that interferes with the conversion of trypsinogen into trypsin or that impedes the passage of the latter to the intestinal foodstuffs cause diabetes? The answer now seems plain, viz.: *because insufficiency of trypsin is followed by imperfect reduction of proteids to simpler bodies, resulting in the formation or inadequate splitting of toxic albuminoids.* In other words, impaired pancreatic action of the kind mentioned gives rise to toxic glycosuria.

Our interpretation of the general subject seems again to conciliate antagonistic views. Indeed, while Lépine[29] has affirmed that "the pancreas exercised a glycolytic influence," Chauveau and Kaufmann have held the opposite: *i.e.*, that "glycolysis is not diminished in diabetes, and that diabetes is exclusively due to an increase in the production of glucose." We have shown that the arterial blood of the pancreas does contain a glycolytic body,—the oxidizing substance,—but we have also—by our analysis of Cartier's paper and other data—demonstrated that suprarenal overactivity was the underlying cause of toxic glycosuria: *i.e.*, a source of increased production of sugar. To further sustain this fact, we may recall that the coal-tar products, as already stated, possess a marked tendency to give rise to suprarenal insufficiency, which sinks sometimes to the stage of blood-disintegration. Lépine has himself observed that methæmoglobinuria could follow the use of antipyrin. This remedy is now classed among the most active agents at our disposal for the reduction of glycosuria. A remark of Professor Lépine's proves this to be the case in another way. Referring to experiments conducted with the collaboration of Porteret, he says, regarding the action of

[29] Lépine: "Le Diabète," Paris, 1899.

antipyrin, that, "in the cases in which it exercises an anti-diabetic action, this substance acts, not by activating the destruction of sugar, but *by preventing its formation*"[30]: the result, *we* would add, of reduced suprarenal activity.

We have made considerable headway in the last few pages. In the first place, we have ascertained (1) that zymogen and trypsinogen were not identical; (2) that the Lépine glycolytic enzyme and the oxidizing substance were the same thing, and, this being the case, that (3) there was no ground for the hypothesis that the islands of Langerhans were the source of the glycolytic substance.

In view of these facts, what is the nature of the product the existence of which the prominent nuclei and the granules observed in the protoplasm of the islands indicate? This is elucidated by two other features just brought out, namely: (4) that glycosuria may be the result of intoxication by toxic albuminoid bodies incident upon an insufficiency of trypsin, and (5) that disease limited to the islands, as shown by Opie, can cause glycosuria. It is plain that, in the latter case, the permeability of the ampullæ being alone compromised, the pancreatic lobules that contain no islands are free as to the elimination of their secretion into the ducts. If they produce trypsinogen,—*i.e.*, trypsin,—why are the functions of the latter inhibited or absent as indicated by the glycosuria? The only logical answer to this question is that *the islands of Langerhans alone secrete trypsinogen.*

This fact, when added to others reviewed, normally leads to another deduction: *i.e.*, that, in addition to any other function it may possess, *the spleen and the islands of Langerhans are functionally united in the formation of a ferment,—trypsin,—which is able to digest albuminoid bodies in the blood-stream.*

We can now readily understand why the spleen and the pancreas are so intimately connected through their nervous supply. Indeed, this throws light upon a phenomenon which we approach almost with diffidence: *i.e.*, Claude Bernard's experimental glycosuria obtained by puncturing the medulla oblongata. "That pathological conditions of the central nerv-

[30] The italics are Professor Lépine's.

ous system and perhaps of the sympathetic and larger peripheral nerves may give rise to glycosuria and diabetes is, of course, established," says Flexner.[31] "The number of neuropathic conditions in which one or the other of these has been found is now considerable. The one definite condition, *the effect of which is constant,* is Claude Bernard's *piqûre,* and, as bearing out the physiological relationship existing between *certain unknown structures* in the floor of the fourth ventricle and the glycogen-store in the liver, may be cited the instances of lesions (hæmorrhages, softening, tumors) in man observed in this situation with which glycosuria has been associated. That cerebral and perhaps spinal disturbances other than those in the region of the fourth ventricle may be associated with or followed by diabetes many clinical cases prove. On the other hand, there is no evidence that would show that it is the direct influence of the central nervous system upon the carbohydrate metabolism that produces hyperglycæmia and glycosuria. Indeed, the experiments in which *the splanchnics were sectioned after piqûre* (Claude Bernard and others) *without producing glycosuria* show the necessity of the interaction of other organs."[32]

Read in the light of all we have said,—particularly the allusion to the relationship between the medulla and the suprarenal glands through the splanchnic,—these lines, from so competent an observer as Flexner, and which confirm those of Cartier as to the action of section of the splanchnic, seem to us to afford confirmatory evidence based upon the most solid labors of the last half-century and to embody Claude Bernard's own sanction. To analyze their far-reaching meaning would involve the repetition of what has been said in all this volume. Formulated as a deduction, the functional relationship between the floor of the fourth ventricle and glycosuria would be as follows: *Puncture of the floor of the fourth ventricle (Claude Bernard) causes glycosuria because the increased blood-supply in the injured area incident upon the local reparative process correspondingly excites the normal structures around this area, which,*

[31] Flexner: *Loc. cit.*

[32] All italics are our own.

in turn, stimulate the adrenals through the communicating branches between the cord and the ganglionic chain.

What we might term the intrinsic functions of the pancreas have now been analyzed; the importance—also in conjunction with the spleen—of its *extrinsic* functions must now be inquired into. Foster states that "a pancreas taken fresh from the body, even during full digestion, *contains but little ready-made ferment,* though there is present in it a body which, by some kind of decomposition, *gives birth to the ferment.*[33] . . . To this body, this mother of the ferment, which has not at present been satisfactorily isolated, but which appears to be a complex body, splitting up into the ferment, which, as we have seen, is, at all events, not certainly a proteid body, and into an undeniably proteid body, the name of *zymogen* has been applied. But it is better to reserve the term zymogen as a generic name for all such bodies as, not being themselves actual ferments, may by internal changes give rise to ferments, —for all 'mothers of ferment,' in fact,—and to give to the particular mother of the pancreatic proteolytic ferment the name trypsinogen." In other words, and in accord with prevailing custom, each zymogen is named from the ferment it produces: the zymogen of trypsin being "trypsinogen"; that of pepsin, "pepsinogen," etc. It is therefore permissible to use the term "amylopsinogen" as the main product of the true lobular acini to differentiate it from trypsinogen, the product of the islands of Langerhans, reserving the term zymogen as a generic term for all pancreatic ferments. As "zymogen" under these conditions, it preserves characteristics attributed to it by Heidenhain; it is soluble in water, in which it is split, after exposure to the air, into trypsin, etc. (Charles). The conversion of trypsinogen into trypsin has been ascribed to oxygen; but if our views are sound and the former is the normal product of the islands, the portion distributed through the pancreatic ducts is intimately combined with the splenic ferment in the ampullæ as fast as formed, so that it can never be obtained as trypsinogen *per se.* Hence, oxygen will split zymogen into trypsin, etc.; but trypsin is not, as stated, oxidized trypsinogen.

[33] These italics are the author's.

We have followed the course of the blood from the splenic vein and back again to the splenic artery which supplies branches to the pancreas, and we have seen that on its way through the latter the arterial blood surrenders its oxygen to the cells and its splenic substance to the islands. The dominant feature of the extrinsic functions of the pancreas is its power to destroy albuminoid toxic bodies, and it is evident that the splenic ferment, the mission of which is merely to unite with trypsinogen to form trypsin, cannot do this alone. It is *trypsin* that constitutes the antitoxic body, and it is the pancreas, therefore, that supplies it to the organism. How does it penetrate the general blood-stream?

Now that we have ascertained that the islands of Langerhans are the seat of manufacture, as it were, of at least a part of this antitoxic agency, and that it collects (combined) in the ampullæ, the manner in which the general circulation becomes supplied with it is clear: *i.e.*, the quantity that permeates through the ampullar walls is but a portion of their contents, and the rest is swept away with the blood and reaches the splenic vein through the pancreatic veins. But this does not mean that trypsinogen may not be carried alone in the same manner to the splenic vein and therein combine with the splenic ferment to form trypsin. In fact, this must constitute the prevailing process, if the anatomical distribution of the islands of Langerhans, as observed by Opie, can serve as guide.

As we have seen, Opie found that the islands of Langerhans were over three times as numerous in the splenic end of the pancreas as elsewhere, and that the part of the organ not in communication with the splenic vein—*i.e.*, the extremity of the descending arm—contained none. Moreover, each lobule in the splenic end of the organ was found to contain an island: a very suggestive fact. The tip of the pancreas, which is almost in contact with the spleen, thus marks the starting-point of the islands; so that trypsinogen begins to enter the splenic vein almost at the hilum. Pancreas and splenic vein being connected by several short venous radicles at about regular intervals, the blood in the vein must become literally saturated with trypsinogen, and its blood be replete with trypsin when it reaches the portal vein, during the active stage of

intestino-portal digestion. We have seen in Herzen's experiment how rapidly albumin was digested with blood obtained from the splenic vein during this stage.

That the amylolytic ferment derived from Heidenhain's zymogen is also carried to the splenic vein is probable. We have seen that it was through the effects of this ferment that the liver glycogen was converted into sugar, and that the importance of the latter, when distributed to the muscles and other structures in which it is consumed, was very great. That the conversion of glycogen into sugar is a continuous process and that it is independent of digestion are recognized facts,—and necessarily so, since the activity of the functions that entail the use of glycogen may at any moment be increased, the tissues requiring replenishment to a correspondingly great degree at the expense of the liver reserve. How could this predominating function be carried on in the perfect manner that it is, were it connected with, or did it depend upon, any digestive process? Again, if present views prevailed and the amylolytic ferment were to only reach the liver after being secreted in the duodenum by the pancreas, then absorbed by the venules of the villi, how could we account for the conversion of glycogen between the periods of active digestion? That the intestinal tract is not the channel traversed by the portion of pancreatic amylopsin devolved to the conversion of glycogen into sugar is also suggested by familiar experiments.

We have seen that the insertion of a piece of pancreas into the tissues of an animal showing marked glycosuria, after removal of the pancreas, will cause it to disappear. This apparently constitutes a direct contradiction of all the foregoing statements; but such is not the case in reality. Minkowski[34] confirmed the fact, observed by other investigators, that glycogen quickly disappears after removal of the pancreas. This indicates two important features: *i.e.*, that glycogen is no longer formed after removal of the pancreas, and that some other agency converts it into sugar. Why removal of the pancreas should prevent the formation of glycogen may probably be accounted for by the fact that the absence of trypsin causes

[34] Minkowski: Berliner klin. Wochenschrift, No. 5, 1892.

the digestion of albumins in the duodenum to cease, as shown in the Schiff-Herzen experiments. That the conversion of food-starches into maltose is also, owing to the absence of amylopsin, arrested, is evident. The only substitute for this ferment available is ptyalin; but though the salivary secretion —at least, its ptyalin—is quantitatively increased after removal of the pancreas, it is inadequate to convert all the starch required to compensate for the glycogen used. The glycogen, gradually converted by what ptyalin is swallowed with the saliva between meals, therefore disappears. The fact that ptyalin converts starch partly into dextrose greatly hastens the disappearance of the glycogen, the primary sugar of which is mainly maltose. It would seem, therefore, *that the glycosuria following extirpation of the pancreas is due to the action of ptyalin upon food-starches.*

That the salivary secretion is gradually increased after removal of the pancreas is sustained by experimental evidence. Aldehoff[35] observed that glycosuria only appeared from 24 to 48 hours after the operation in turtles; in frogs it only appeared after four or five days, "slight at first, becoming more intense later on." Minkowski[36] found that it sets in after two or three days in dogs, under the same conditions. Again, during its passage through the stomach ptyalin acquires increased energy as a ferment. Charles[37] refers to this question as follows: "Chittenden and Griswold find that the presence of acid, as hydrochloric acid, to the amount of 0.005 per cent. decidedly increases the diastatic action, while an increase beyond this diminishes it, the action stopping with solutions of acid from 0.1 to 0.4 per cent.; the diastatic action of the saliva would, therefore, appear soon to cease in the stomach, but *the peptones* in that organ exercise a decided influence on salivary digestion, stimulating the ferment to *increased action*, particularly in presence of acid, which by itself may completely prevent the conversion of starch into sugar." Mering found that starch acted on by saliva yielded dextrin and maltose at first, then after some time grape-sugar.

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[35] Aldehoff: Zeitschrift für Biologie, Munich, Bd. xxviii, p. 293, 1892.
[36] Minkowski: *Loc. cit.*
[37] Charles: *Loc. cit.*

Yet, glycosuria so produced may, we have seen, be prevented by grafting a fragment of pancreas under the skin. Minkowski[38] grafted such fragments in the dog, cat, and pig, removed from the pancreas of these animals. When the graft had become adherent and functionally active, he removed the rest of the pancreas. No glycosuria appeared until the grafted portion itself had been removed. Besides indicating that ptyalin glycosuria prevails after resection of the pancreas, the fact that grafts can preserve normal functions clearly shows that the intestinal canal is not the only region wherein splitting of carbohydrates and proteids may occur. Each graft evidently received its blood through newly-formed vessels. This blood doubtless contained splenic ferment, since, as previously stated, the greater portion of this ferment really enters the general circulation *via* the liver, and ultimately reaches the portal circulation, probably by the hepatic artery, in the experimental animals. Such being the case, it is evident that *the splenic vein can, besides the intestinal villi, serve as a channel for the transmission of the pancreatic and splenic ferments to the liver.*

Here, again, however, are we brought to realize that the splenic ferment is not merely a local agency, but one which during spleno-pancreatic activity forms part of the entire blood-stream. We have given striking evidence of this in Herzen's experiment with blood taken from various arteries and veins. We saw that blood taken from the femoral vessels (arterial and venous) of a dog in full splenic digestion proved active in digesting albumin, and that the blood of the splenic vein was exceedingly active. Indeed, the blood which is so active in the pancreas originates from the cœliac axis, lungs, heart, etc.,—*i.e.*, from the general circulation,—and only contains the proportion of splenic ferment which the entire blood-stream contains. But a question suggests itself here: If, by the combination of trypsinogen and the splenic ferment, trypsin is formed, is it not trypsin-laden blood that re-enters the pancreas? Trypsin *would* re-enter this organ were the relative proportions of the two bodies not regulated by the vagus. As

[38] Minkowski: *Loc. cit.*

we find that a slight excess of splenic ferment will serve the physiological process in the pancreas,—to supply the intestinal canal,—if we grant the vagus even one-tenth of the truly wonderful prerogatives it seems to possess, we can readily assume that, by regulating the quantities of either ferment allowed to enter the blood-stream, it provides just the excess of splenic ferment in the pancreas to insure perfect function during the digestive process: all features which indicate that *trypsin is a constituent of the entire blood-stream when albuminoids are undergoing digestion in the alimentary channels.*

The far-reaching meaning of all this is suggested in the following deductions:—

1. The cleavage processes to which trypsin submits albumins in the intestinal canal include the preliminary steps of a protective function.

2. The spleno-pancreatic internal secretion is represented by the trypsin which reaches the portal vein by way of the splenic vein, and which continues in the blood-stream the cleavage processes begun in the intestinal canal.

3. The main function of the spleno-pancreatic secretion, trypsin, in the blood-stream is to protect the organism from the effects of the toxic derivatives of albuminoid bodies.

CHAPTER IX.

THE ADRENAL AND VAGAL SYSTEMS IN THEIR RELATIONS TO CARDIAC AND PULMONARY FUNCTIONS.

We have repeatedly referred to the functional connection between the secretion of the adrenals and the heart. Is this connection direct or is it indirect? In other words, is it the result of a direct stimulation of the heart-muscle such as is produced by suprarenal extract, or of the stimulating effect to which the increase of oxidizing processes, including those of the cardiac cerebro-spinal centers, give rise? Analysis of this question tends to show that both processes prevail simultaneously when from any cause the adrenals become overactive.

THE ADRENAL SECRETION AS THE SOURCE OF THE FUNCTIONAL ACTIVITY OF THE RIGHT HEART.

As freshly-oxidized blood is constantly being supplied to *both* sides of the heart, the specific action of digitalis upon the right heart to which we have referred cannot be ascribed to the oxidizing substance. Again, it would seem that the suprarenal secretion itself could hardly be credited with a local stimulating action upon the cardiac walls when the thickness of the myocardium is recalled, unless the latter be provided with channels calculated to insure the penetration of the secretion to its deeper tissues. Not only do such channels exist, however, but they are so disposed as to enable the adrenal active principle to permeate the entire myocardium and be equally distributed among the contractile elements. The channels to which we ascribe such important functions have been known as the "foramina of Thebesius."

These canals are described in Gray's "Anatomy" as follows: "The foramina Thebesii are numerous minute apertures, the mouths of small veins (venæ cardis minimæ), which *open* on various parts of the inner surface of the auricle. They *return* the blood directly from the muscular substance of the

heart. Some of these foramina are minute depressions in the walls of the heart, presenting a closed extremity."[1] This information would afford but little light could we not supplement it with an excellent paper by F. H. Pratt,[2] in which the *nutrition* of the heart through the vessels of Thebesius and the coronary veins is studied. How much we are indebted to the author for his investigations is suggested by the following remarks: "So far as I have been able to determine, no *experimental* physiological work has ever before been done on the vessels of Thebesius; all opinion regarding their functional importance has rested upon the assumption that they only serve as veins, conveying a part of the venous blood from the coronary capillaries through the foramina Thebesii into the cavities of the heart."

After referring to the labors of Thebesius (1708), Vieussens (1757), Haller (1786), and Abernethy (1798), the author reviews the more modern investigations of Bochdalek,[3] which led to the conclusion "that the greater number of the small openings on the inner surface of the right as well as the left auricle, which from early times have borne the name of foramina Thebesii, represent the mouths of little veins that, *often uniting into larger vessels,* course with many branches *through the auricular walls.*" Langer's researches[4] on the foramina of the human heart are next analyzed. "With the aid of the blow-pipe, and by means of a watery injection-mass colored with Berlin blue, he demonstrated these foramina *in all the cavities* of the heart. He succeeded in injecting the vessels of Thebesius not only from the coronary vessels, but from the *endocardial* surfaces as well. Bochdalek's observations regarding the presence in both auricles of foramina Thebesii were thus confirmed, and the fact of a communication between the coronary vessels and each of the four cavities of the heart was thoroughly established. The foramina which Langer found on the endocardial surfaces of both ventricles were similar to those in the auricles, but much smaller. They

[1] All italics are our own.

[2] F. H. Pratt: American Journal of Physiology, vol. i, p. 86, 1898.

[3] Bochdalek: Archiv für Anat. u. Phys. u. wiss. Med., Leipzig, p. 314, 1868.

[4] Langer: Sitzb. der k. Akad. der Wissensch. zu Wien, 1880, Bd. lxxxii, 3 Abth., p. 25.

were most conspicuous on the papillary muscles and in the *neighborhood of the great vessels,* being less easily seen in the region of the apex, where they were obscured by the trabecular net-work."

Very suggestive in connection with our own views are also the observations of Gad[5] on the vessels of Thebesius in the ox, and to which Pratt refers in the following words: "In the method which he describes for demonstrating the action of the valves of the *left* heart, wherein water under pressure is made to fill the ventricle and aorta, he noticed that water flowed into the *right* heart from the foramina Thebesii. On illuminating the interior of the left ventricle he was enabled to see fine, blood-stained streams issuing from the endocardial wall into the clear water with which the cavity was filled." Finally he reviews the labors of Magrath and Kennedy,[6] who, "working with artificial circulations of defibrinated blood on the isolated heart of the cat, observed that a small portion of the *coronary blood* found its way into the *left ventricle.* The only possible source of access other than from the vessels of Thebesius was leakage past the aortic valves. This leakage, as shown by a manometer-record of aortic pressure, did not occur." The author closes his review of the literature of the subject with the statement that "notwithstanding these painstaking observations, the vessels of Thebesius still occupy a very obscure position in anatomical literature. Foramina Thebesii are referred to as constant in the right auricle, forming in part the mouths of small veins. Their occurrence in the left auricle is occasionally mentioned. But the fact that *the vessels of Thebesius open into all the chambers of the heart*—ventricles as well as auricles—is hardly recognized."[7]

In the author's own experiments, various agents were injected at a constant pressure, through the coronaries of fresh, often still living, hearts of the rabbit and dog. They showed that liquids in these vessels penetrate into the heart cavities through the endocardial foramina, thus verifying the foregoing

[5] Gad: Archiv für Physiologie, p. 380, 1886.

[6] Magrath and Kennedy: Journal of Experimental Medicine, vol. ii, p. 13, 1897.

[7] All italics are our own.

data. As the cannula was tied directly into the artery, the liquid could only reach the cavities through the foramina, while in all experiments care was taken to avoid high pressures. In the heart of the ox the endocardial depressions were found "regularly *larger in the auricles* than in the ventricles," while in the right auricle "they may," he states, "be provided with thin, single valves, *especially about the origin of the great veins.*" In the left auricle the depressions are fewer in number and unprovided with valves. "Foramina Thebesii are *never absent from the ventricles,*" says Dr. Pratt. "In the *right* ventricle, which is *especially well provided with them,* the larger number are seen upon the septal wall. It is often *much more difficult to find them in the left ventricle,* although a diligent search is never without a reward" . . . "structures, accessory to these ventricular foramina, which might in any way serve the office of valves I have not seen." . . . "On the injection of the vessels of Thebesius with air by means of the blow-pipe applied to the foramina, characteristic, fine, *subendocardial ramifications,* which very frequently conduct the air into other Thebesian systems, or *even into the great coronary veins* will seldom fail to appear." The latter point is also sustained by experimental evidence.

The fact that the right side of the heart is endowed with a more perfect system of canalization than the left is suggested by the following remarks: "The ease with which injections of air and blood could be made to demonstrate the connection between the vessels of Thebesius and the coronary veins caused me to doubt the opinion expressed by Langer that the foramina Thebesii in the ventricles *communicate with the veins by capillaries alone.* To settle this point, I injected the coronary veins of the ox with starch and celloidin masses, both too thick to pass the capillaries, and found that even these emerged from the foramina Thebesii of the right ventricle. So intimate a connection, however, between the coronary veins and the vessels entering the *left ventricle I have not yet been able to demonstrate.*" The author also says: "By means of a very successful corrosion preparation, made by injecting the veins of an ox-heart with celloidin, I was able to trace the communication. In this preparation the position of some of the foramina

Thebesii was marked by small disks of the hardened mass formed by the oozing out of the celloidin upon the endocardium. These foramina were shown to be connected with the smaller *coronary veins* by fine branches. The still finer ramifications which, as Langer has demonstrated, lead from the foramina and branch directly into capillaries were here uninjected; they would appear only when injected from the foramina themselves."

The only connection between the vessels of Thebesius and the coronary arteries that he could find, notwithstanding repeated attempts, was by capillaries. Bochdalek having observed that the foramina of one auricle communicated with those of the other, he was able by blow-pipe injection to verify the correctness of this view, the air of one auricle having passed out through a similar exit into the other.

To sustain his view that the nutrition of the heart may be carried through the vessels of Thebesius some time after the coronary arteries are absolutely obliterated, a number of experiments are related. Thus, fluid introduced into the ventricle of an isolated heart, by means of a cannula passed down to this cavity, and tightly held *in situ* by a ligature passed around the auriculo-ventricular groove, only found its way through the vessels of Thebesius. Defibrinated blood, inserted into the organ through this cannula, brought on, often within one minute, "strongly marked, co-ordinated contraction of the ventricle." As the blood thus introduced would become venous, the action would become gradually reduced, but renewal of the blood would at once cause the heart to resume its normal action. "With a periodic supply of blood," says the author, "and with favorable temperature and moisture this may continue several hours." That mere mechanical stimulation by distension did not cause the phenomena witnessed is demonstrated by the alternate use of Ringer's solution and defibrinated blood. While the solution failed to sustain contractions, blood always succeeded.

Another experiment served to demonstrate that a true circulation could take place between the vessels of Thebesius and the coronary veins. The organ being disposed as stated above, two of the coronary *veins* were incised; "a small, but

steady, stream of venous blood issued from them." Under the same conditions the descending branch of the left coronary *artery* was opened. "No flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein." In still another experiment the trunks of both coronary arteries were ligated and the ligature around the ventricles omitted. "The supply-cannula was tied into the ventricle through the aorta. On the introduction of blood the left ventricle alone began to beat strongly and regularly . . . the blood found its way in part into the right ventricle, coming of necessity through the walls. . . ." The blood from the left ventricle had thus found its way into the right one. Finally, he refers to the striking analogy which this nutritional system presents to that of the frog and cat. In the frog the heart is almost entirely nourished "through the branching passages that carry the blood from the interior of the heart nearly to the pericardial surface."

On the strength of all this evidence, Dr. Pratt concludes (giving only the features that bear directly upon the question we are analyzing) that: "1. The vessels of Thebesius open from the ventricles and auricles into a system of fine branches that communicate with the coronary arteries and veins by means of capillaries, and with the veins—but not with the arteries—by passages of somewhat larger size. 2. These vessels are capable of bringing from the ventricular cavities to the heart-muscle sufficient nutriment to maintain long-continued, rhythmic contractions. 3. The heart may also be effectively nourished by means of a flow of blood from the auricle back into the coronary sinus and veins." The author concludes with the very appropriate remark: "It is evident that the nutrition through the vessels of Thebesius and the coronary veins must modify in no slight degree the existing views of the nutrition of the mammalian heart, and of the manner in which infarction of the heart takes place." The clinical features of this question will be considered elsewhere.

Viewed from our standpoint, *the vessels of Thebesius are more concerned with the dynamics of the heart than with the nutrition of this organ*, though the latter function is not to be ignored, particularly in the sense emphasized by Pratt: *i.e.*,

as a source of compensation. That nutrition of the left heart, auricle and ventricle, constantly filled with arterial blood, can result from a flow of the latter through the Thebesian vessels seems clear, but nutrition can hardly be associated with a similar process in the *right* heart, with nothing but *venous* blood to propel through the Thebesian channels. That nutrition, the recognized prerogative of arterial blood, owing to its oxygen, cannot be the active factor here is evident.

The right heart seems, judging from the anatomical arrangement of the parts concerned in the process, to play a physiological function of a special kind. While the Thebesian openings are larger in the auricles than in the ventricles, in the left auricle they are also fewer than in the right; but even more suggestive is the fact that, while some openings in the right auricle are supplied with valves, none have been found in those of the left. Again, both ventricles are supplied with foramina; the right ventricle is particularly well provided with them, while they are difficult to find in the left one. That the septal wall should show them most clearly on the right side is also suggestive. Evidently a similar condition exists between the auricles, as suggested by Bochdalek and confirmed by Pratt; but the fact that limited information supplied by works on anatomy usually covers only those of the right auricle points to greater prominence of the latter. Thus, Gray[8] states that the venæ Thebesii open "on the inner surface of the right auricle." Finally, the openings supplied with valves are in the right auricle, as we have seen; but they are also stated to be most conspicuous in the neighborhood of the great vessels; hence it must only be the Thebesian openings around the great vessels of the right auricle—the venæ cavæ and the pulmonary artery—that are provided with valves.

If we can now ascertain whether the current which enters the Thebesian vessels from the right auricle is shut *out* in this location, or secured *within* the channels, according to the manner in which the valves close,—*i.e.*, inwardly or outwardly,—we will be able to decide whether *venous* blood from the venæ

[8] Gray: "Anatomy"; edition, 1901, p. 622.

cavæ or arterial blood from the lungs circulates in the Thebesian system.

Bochdalek found that many of these openings in the auricles "presented the appearance of blind depressions, since they were often covered with single valves in such a way as to resist investigation with the blow-pipe" . . . "some were slit-like, resembling the mouths of the ureters; still others were large, round depressions, with smaller openings at the bottom." The first remark suggests that the openings serve as exits into the auricle, while the second points to the contrary, since it is difficult to conceive of a *depression* with "openings at the bottom" as a valve calculated to resist liquids exerting pressure on the concave side. From the left auricle Gad caused water to pass out of the right and left ventricular walls, but, as the auricular openings have no valves, this only serves to emphasize the extensive canalization which the Thebesian system represents. The system might, therefore, be considered as essentially calculated to distribute venous blood from the right auricle to the entire heart: a fact which the free anastomosis with the venous channels would seem to sustain.

Pratt states that he has seen "structures accessory to these *ventricular* foramina which might in any way serve the office of valves" . . . "the edge of the foramen is usually sharply defined and may frequently exist as a partial, *shelf-like*, covering, giving the impression perhaps of an attempt at a membranous valve; but it is seldom more than this." A shelf means a projection, and the fact that it is membranous suggests that during ventricular *contraction* this valve is pressed against the opening and closes it: a feature which involves the possibility that during diastole a current—whether venous or arterial—flows into the ventricle through its foramina. That the latter and their valves open inwardly—*i.e.*, in the ventricle—is demonstrated by Pratt's experiment, in which he injected the coronary *veins* with starch and celloidin and found that even these passed *into* the ventricle. If, therefore, the venous blood of the right heart at all enters the muscular *walls* it is not through the foramina of the ventricle, *i.e.*, from below; it must be through the openings above, *i.e.*, those in

the right auricle. The experiment in which the cannula was tied in the pulmonary artery, the blood being "allowed to enter the right auricle through insufficiency of the tricuspid," appears to us to further sustain this fact. The heart continued "its rhythmic contractions for eight hours: a period considerably in excess of that observed in nutrition through the vessels of Thebesius alone. It was inferred that blood had gained access from the auricle to the coronary veins and had thus aided materially in the nutrition." While this course may have been taken by some of the blood in the experiment, it is obviously not a normal one during life, and the unusual duration of the contractions seems to us to indicate that the blood that penetrated into the right auricle found its way into the Thebesian system *via* the openings in this auricle, thus approximating as nearly as possible normal conditions.

The relations between the coronary veins and the Thebesian channels are self-evident, excepting, however, a theoretical back-flow from the auricles into the veins suggested by Pratt, which appears to us abnormal; at least it is not compatible with our views of the process. The Thebesian vessels and coronary veins were found to communicate freely on the right side, but not on the left, with the ventricular foramina. The septal foramina were also found to communicate with the coronary vein at the end of the sinus. An interesting feature is the fact that blood passed into the right ventricle flowed freely from a cut vein of the *left* heart (experiment of April 3, 1897). On the other hand, the relations between the coronary arteries and the Thebesian vessels are of a peculiar kind; thus the communication between the *left* coronary artery and the *right* ventricle seems as free as that between the same artery and the *left* ventricle (through the Thebesian channel) is limited. The experiment in which a colored solution was passed into the left coronary artery caused an accumulation of 400 cubic centimeters to flow from the right ventricle, while only 4 cubic centimeters flowed from the left, sufficiently emphasizes this fact. Haller, who had observed that injected substances flowed out freely from the surfaces of both ventricles, states that "the passage from the arteries into the cavities of the left side is more difficult."

All these features seem to fully supply the needs of the function with which the secretion of the suprarenal glands must be connected, if the phenomena witnessed in many disorders and after the use of most remedies have been correctly interpreted. That we are in the presence of a dual process of which the suprarenal secretion, operating in the right heart, and the arterialized blood in the left heart are active factors seems probable. Again, the marked power of arterial blood —or rather of plasma—since the defibrinated blood filtered through cotton was used—to sustain functional activity, even when only poured into the ventricles, as shown by Pratt, certainly indicates that the blood must alone be able, during life, to compensate, in case of need, for insufficiency of blood furnished by the coronary arteries.

The contractions of the *left heart* seem to us to be greatly assisted by the arterial blood that enters it, and mainly by that which enters the cavities themselves. The experiments of Pratt having shown that contraction could be produced by contact with arterialized blood, the arrival into the *auricle* of a normal quantity of this fluid must be fully capable, therefore, of causing contraction of the walls of that cavity. The relations of the several structures and the mechanism involved seems to us to be as follows: The main structures upon which the arterial blood reacts are (1) the musculi pectinati and (2) the sinus venosus and appendix auriculæ, all of which are so disposed as to offer as much surface as possible to the blood. The walls of the cavities mentioned are provided with numerous channels, the Thebesian "veins," to satisfy this purpose. The blood which enters the auricle when it is dilated penetrates all the circuitous areas around the musculi pectinati and into the Thebesian vessels, and the ensuing contraction forces the blood-plasma into the smaller subdivisions of these vessels, from which they find their way into the auricular veins. When the arterial blood reaches the *ventricle*, a process similar to the preceding occurs. The columnæ carneæ are disposed so as to offer considerable surface to the blood, while the ventricular walls are permeated with Thebesian channels, into which the blood penetrates during diastole. The contraction induced closes the apertures of these channels, and forces the blood-

plasma into their smaller ramifications and finally into the veins. The larger channels carry the corpuscular elements to the latter. The rôle of the coronary arteries will be referred to later on.

The *right heart,* as we view the process, owes its functional activity mainly to the suprarenal secretion brought to the cavities by the vena cava. We have sufficiently emphasized the power of this agent to restore cardiac action and sustain it even when the entire spinal cord has been obliterated. The manner in which it exercises its powers is similar to that of the arterial blood on the left side. On penetrating the auricle the contractile structures are submitted to its immediate effects; but the orifices of the Thebesian vessels or channels are more numerous and larger than in the left auricle. The membranous edges previously referred to as valves by the investigators quoted do not appear to us to merit being considered as such after careful examination of these structures in the ox-heart. The aperture being closed by the least squeezing of the tissues containing them, it seems evident that they should as readily close under the powerful contraction of the auricular tissues. The right ventricle also presents a very much larger number of Thebesian orifices than the left, while its walls, though thinner, plainly show the ramifications of these channels. That the venous blood charged with suprarenal secretion should at once penetrate the latter when the ventricle begins to contract is self-evident. Return of the blood to the circulation is effected in the same way as in the case of the left heart: *i.e.,* through the coronary veins.

The whole process is an exceedingly uncomplicated one, but, as we will see later on, it simplifies many obscure problems, while affording, in connection with the coronary arterial blood, a supply in keeping with the vital importance of the organ itself. Again, Dr. Pratt's experiment, in which blood injected into the *left* auricle flowed freely from the right ventricle, emphasized the possibility of compensation in case of need. Thus, while under normal conditions, the pressure in both ventricles must be equal, reduced contraction—of the right ventricle, for example—through insufficiency of the adrenals would automatically cause the arrival into it, through

the Thebesian foramina of the septum, of at least some arterial blood. That this does not always suffice to maintain interventricular equilibrium, however, is illustrated by the dicrotic pulse, the pulsus paradoxus, and other kindred phenomena.

Suggestive in this connection are the remarks of Professor Porter in his review of the subject of cardiac innervation in the "American Text-book of Physiology"[9]: "A positive demonstration that the nerve-cells in the heart are not essential to its contractions," says this observer, "is secured by removing the tip of the ventricle of the dog's heart and supplying it with warm defibrinated blood through a cannula tied into its nutrient artery. Long-continued, rhythmical, spontaneous contractions are thus obtained (Porter[10]). As the part removed contains no nerve-cells, the observed contractions can only arise in the muscular tissue, provided we make the (at present) safe assumption that the nerve-fibers do not originate impulses capable of inducing rhythmic muscular contractions." As will be shown, the cardiac nerve-fibers, as in all the organs we have reviewed, merely impose upon the muscular fiber the required *vibratory* rhythm. This is well illustrated by the following experiment: If the apex of a frog's heart "is suspended in normal solution," says the same author, "and a constant electric current kept passing through it, beats will appear after a time, the frequency of pulsation increasing *with the strength of the current*" (Langendorff[11]). But Porter also remarks, almost prophetically in the light of our views: "The demonstration that the nerve-cells are not essential to contraction places us one step nearer the true cause of contraction. It is some agency *acting on the contractile substance.*[12] Evidence is accumulating that this agent is a *chemical substance*, or substances, *brought to the contractile matter by the blood.*"

That the "chemical substance brought to the contractile matter by the blood" is represented by the adrenal secretion and the oxidizing substance seems clear.

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[9] Porter: "American Text-book of Physiology," second edition, 1900.
[10] Porter: Journal of Experimental Medicine, vol. ii, p. 391, 1897.
[11] Langendorff: Archiv für gesammte Physiol., lxi, p. 336, 1895.
[12] All italics are our own.

THE ACTION OF THE ADRENAL SECRETION AND THE OXIDIZING SUBSTANCE UPON THE CARDIAC MUSCLE.

The histology of the myocardium still offers a broad field for conjecture, notwithstanding the many investigations to which it has been submitted by modern observers. The known facts are briefly these: Its tissue is composed, in man, of short, round fasciculi, or bundles, of striated fibers, possessed of thick lateral projections. The latter directly connecting with a similar projection of the adjoining bundles and being cemented to it, a thick close-meshed net-work is formed: a characteristic of the heart-muscle. But it differs from other muscles in several other particulars; its fibers are one-third smaller and their striæ are much more faint; they possess no sarcolemma and are, therefore, exposed to the immediate action of a fluid that may surround them. The manner in which the contractile structures are combined in bundles is also peculiar: each bundle is made up of central prismatic fasciculi of round fibers, in which nuclei (one or two) with their surrounding protoplasmic area are imbedded, the whole being surrounded with flat or ribbon-like columns of muscle-fibers. The perinuclear protoplasm referred to generally contains fat-droplets and *minute pigment-granules* which resemble hæmoglobin, and sends projections between the surrounding muscular fibers so that each of the latter is connected with and is only separated from its neighbor by a layer of protoplasm. This arrangement does not in any way modify the manner in which the sarcous elements are disposed, while the disks, clear spaces, etc., are precisely as they are elsewhere in the organism. These muscular "primary" bundles form, by their union with one or two of their neighbors, columns, or chains—or "secondary" bundles, which are covered, as shown by Ranvier, with a sheath of loose connective-tissue cells, which cells, in turn, connect with one another by numerous projections, or extensions. The primary fasciculi also contain connective-tissue sheaths which invest the muscle-fibers and are likewise supplied with connective-tissue cells. All this forms a close, though permeable, net-work, which makes it possible for a liquid to penetrate the muscular columns or chains and come into direct contact with the bare, or exposed, muscle-fiber.

Indeed, the intimate structure of the myocardium precisely supplies the required structure for the equable and free distribution of such an agency as the suprarenal secretion represents. Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. These canals—the lacunæ of Henle—are the intervals between the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the lymphatic vessels, the lacunæ have been considered as adjuncts, or extensions, of the latter.

Renaut,[13] however, concluded that the penetration of the colored fluids into the lymphatics merely demonstrated the weak resistance of the endothelial coat of the latter, and the spaces, or lacunæ, of Henle being unprovided with endothelial walls, there was no ground for the prevailing belief that they represented lymphatic vessels. He found that all the lymphatic capillaries of the myocardium are located on the surface of the heart underneath the pericardium. They are large and bosselated and form a mesh-work which covers the whole cardiac surface, and send smaller blind pouches into the muscular interstices. The spaces of Henle should be considered, he thinks, "not as true lymphatic cavities analogous to those observed around the pulmonary lobules of certain animals, but as mere connective-tissue spaces, which represent, in fact, pathways for lymph." In a foot-note Berdal states that the spaces of Henle are crossed by "vessels," and in the text the following remark as to the identity of this lymph appears: "The muscular fibers of the heart are thus bathed in connective-tissue spaces in which lymph easily circulates; but this lymph is not that of the lymphatic vessels or capillaries, but that of loose connective-tissue spaces (Renaut)." It is needless to state that this suggests the presence of blood-plasma. Still, we can only consider this deduction as tentative.

[13] Renaut: Traité d'Histologie pratique, p. 719; quoted by Berdal, *loc. cit.*, p. 285.

The manner in which the blood-plasma, whether venous or arterial, is distributed by the Thebesian channels is well shown in a study of the vessels of the heart by Arthur V. Meigs.[14] The extreme paucity of literature on the Thebesian channels has caused them to be overlooked by practically all histologists; that they should be treated as capillaries in the author's paper is, therefore, as normal as it is for text-books to do so. "The capillaries of the human heart," says Dr. Meigs, "differ in two ways from those of other parts of the body: they penetrate the muscular fibers, and some of them are larger than those found elsewhere, and of different arrangement. . . . The accompanying illustrations are drawings which were made with the camera lucida. They are from sections of two human hearts. The first is from the heart of a negro woman, 40 years old, who died of burns. Some pieces of the organ were preserved in Fleming's solution, and others in 70-per-cent. alcohol, and they were stained in bulk with borax-carmine and imbedded in paraffin. The second heart is that of a man, 30 years old, who died of lead encephalopathy. When the post-mortem examination was made, the heart being still quite fresh, there was injected through each of the two coronary arteries as much as the blood-vessels would easily receive of a solution of 3 grammes of Berlin blue (Grübler's) in 600 cubic centimeters of water. Pieces of the organ of suitable size were at once placed in preservative fluid, some in 70-per-cent. alcohol, and others in formaldehyde solution. The tissue was afterward stained in bulk with borax-carmine and imbedded in paraffin.

"The penetration of the muscular fibers by the capillaries is made perfectly clear by the illustrations; it is shown as well by the injected as by the uninjected heart. The two methods of demonstration supplement one another, because, in injected tissue which has been stained, the blood-vessels and their situation are made very obvious by the contrast of color, but the details of the structure of the walls are obscured by the injection material, while, on the other hand, in the uninjected tissue, the structure of the blood-vessels can be seen with the utmost distinctness. In Figs. 1 to 4 the capillaries are easily recog-

[14] Arthur V. Meigs: Journal of Anatomy and Physiology, Jan., 1899.

nized. Their situations in relation to the muscular fibers are very varied. Some are in the intermuscular fibers, others slightly indent the sides of the fibers; still others are within the fibers close to their peripheries, and sometimes the capillaries are in the very centers of the fibers. This penetration of the muscular fibers of the human heart in the adult is a most

DESCRIPTION OF DR. MEIGS'S PLATE.

"Scales are included with the plate, showing the amplification. [The amplification has been reduced about one-third in the reproduction herein presented.]

"Fig. 1.—x 420. From a man, 30 years old, who died of lead encephalopathy. A section of papillary muscle of the heart cut across the fibers. *bb* are injected capillaries, the one partially and the other entirely within the muscular fibers. *c*, A capillary which remains uninjected; its nucleus is included.

"Fig. 2.—x 420. From the same tissue as Fig. 1. *v*, A vein stained by the injection material. *bb*, Capillaries whose precise situation cannot be defined. They cannot be said to be intermuscular spaces, nor to be entirely within fibers. The effect is as if the fibers were coalescing.

"Fig. 3.—x 420. From the same tissue as Fig. 1. *f*, A capillary in a fiber. *g*, A capillary in the center of a very small fiber. This is perhaps the most convincing instance of the penetration of a muscular fiber by a capillary.

"Fig. 4.—x 420. A section of heart cut transversely to the muscular fibers, from a negro woman, 40 years old, who died of burns. The muscular fibers are of irregular shape. *d*, A capillary within a muscular fiber, its nucleus upon one side producing a resemblance to a seal ring. *e*, A capillary within a muscular fiber. *f*, A capillary in an intermuscular space; its nucleus being included, it resembles a seal ring. *g*, A capillary in an intermuscular space; its endothelial wall appears as a simple circle.

"Fig. 5.—x 115. From the same tissue as Fig. 4. A large capillary, receiving many branches and surrounded by muscular tissue. The capillary and its branches are almost filled with blood-corpuscles. The capillary walls are distinctly visible, containing many flattened endothelial nuclei.

"Fig. 6.—x 42. From the same tissue as Fig. 1. Not printed in two colors, because the essentials show equally well in black. *m*, Muscular tissue. *a*, An arteriole; the solid black within its caliber is injection material. *v*, The accompanying vein to the arteriole, *a*; it also contained a little of the injection material; these two vessels are in a connective-tissue interspace. *c*, A large capillary; it contains a good deal of the blue injection material, which is represented by the heavily-shaded portions. These three vessels—arteriole, vein, and capillary—give a good idea of the character of such vessels in the heart. The great size of the capillary is the most striking feature."

striking and curious phenomenon, and it does not exist at an early embryological stage. The condition is, therefore, one of later development, but it is not yet known at how early an age it does exist . . . . . .

"Very large capillaries are found in the human heart, and such vessels are shown by Figs. 5 and 6. It is not common to find minute veins in company with the arterioles in the deepest

Fig. 1.

Fig. 2.

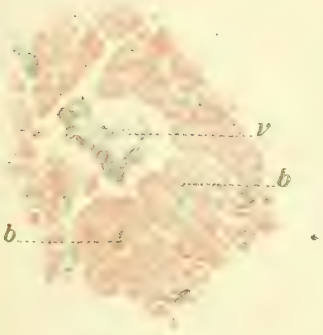


Fig. 3.

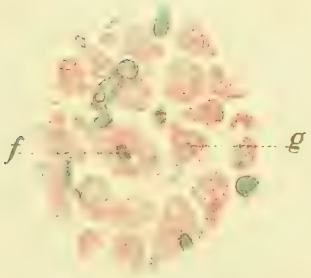


Fig. 4.

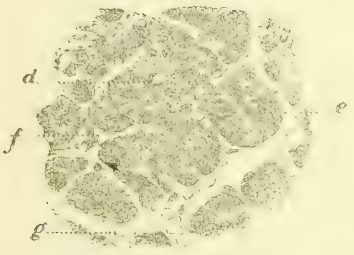


Fig. 5.

Fig. 6

portions of the muscular substance of the heart, although it is well known that, upon the surface and in the connective-tissue interstices, arteries are found with their venæ comites, just as they are in other organs and tissues. The arrangement of the vessels upon the surface and in the interstices is in marked contrast with that found in the muscular substance proper. Here, when an arteriole is accompanied by an efferent vessel, this vessel is single coated and composed of endothelium, being exactly like the smallest capillaries, except in size. These peculiar large capillaries are found not only in company with arterioles, and, therefore, when carrying on the function usually performed by veins, but also alone. When they are alone, it is impossible to be certain whether their function was afferent or efferent. It may well be that arterioles are less numerous in the heart than in other tissues, and that their place is taken by the large capillaries. These capillaries are so numerous and of such size that it seems likely they perform the function of reservoirs. The presence of the large capillaries and the penetration of the muscular fibers by the capillaries indicate a provision for the blood-supply of the heart even more bountiful than that of the other organs."

That these vessels are the Thebesian channels is evident; their mode of distribution and the peculiar endings of their subdivisions is particularly well shown in Fig. 6, while the outpouring of plasma for absorption by the muscle-elements is suggested by Fig. 5.

The fact that the distribution of the Thebesian channels is analogous to that observed in the heart of the frog has, we have seen, been noted by Pratt. This had also been noticed by Lannelongue, but this author considered the channels of the human myocardium as vestiges of the batrachian system. Berdal, who alludes to the latter, states that in the frog and in the batrachian *urodela* there are no ordinary blood-vessels. "The muscular fasciculi intercept cavernous spaces into which the blood penetrates directly and from which they are only separated by endothelium. *The frog's heart is thus a true sponge the structures of which, formed of muscular fibers, nourish themselves by imbibition.* In mammals, on the contrary, the myocardium contains distinct vessels. The capillaries form a net-work the

meshes of which, elongated and parallel to the muscular fasciculi, are connected by short branches, which give each mesh the appearance of a parallelogram. When these vessels cross the spaces of Henle, they are covered, on the external surface, with flat connective-tissue plates." Pratt's observation not only includes the analogy between the human lung and that of the frog, but also with that of the cat, a mammal. Under these conditions, it becomes clear that in man, also, *the heart-muscle may be regarded as a sponge-like structure, the contractile elements of which are nourished and supplied with working energy by substances in the blood-plasma.*

What is the rôle of the blood of the coronary arteries in the functions of the heart? This may perhaps be traced by analyzing the effects of ligation of these arteries upon these functions. Porter[15] refers as follows to the experimental work in this connection: "The frequency of arrest after ligation is in proportion to the size of the artery ligated, and hence to the size of the area made anæmic, and is not in proportion to the injury done in the preparation of the artery. The circumflex and descendens may be prepared without injuring a single muscle-fiber, yet their ligation frequently arrests the heart, while the ligation of the arteria septi, which cannot be prepared without injuring the muscle-substance, does not arrest the heart. It is, moreover, possible to close a coronary artery without mechanical injury. Lycopodium-spores mixed with defibrinated blood are injected into the arch of the aorta during the momentary closure of that vessel and are carried into the coronary arteries: the only way left open for the blood. The lycopodium-spores plug up the finer branches of the coronary vessels. The coronary arteries are thus closed without the operator having touched the heart. Prompt arrest, with tumultuous fibrillary contraction, follows."

If the plasma that reaches the heart by way of the Thebesian channels can sustain both its nutrition and its contractions, how can such results as these be accounted for? The sudden arrest of the heart's action by plugging the coronary arteries certainly points to a predominating function, and, more than this, to a function of which they are alone the sources of blood-

[15] Porter: *Loc. cit.*

supply. That the rôle of the coronary blood is precisely that which obtains elsewhere in the organism is forcibly suggested by the experiments of Langendorff, who was able, according to Porter, "by circulating warmed *oxygenated defibrinated* blood through the coronary vessels, to maintain the hearts of rabbits, cats, and dogs in activity after their total extirpation from the body." It is clear that the blood-plasma can incite functional activity when introduced through the coronaries as well as when introduced into the ventricles. "Even pieces removed from the ventricle will contract for hours," continues the author, "if fed with blood through a cannula in the branch of the coronary artery which supplies them (Porter[16]). It is evident, therefore, that the cause of the rhythmic beat of the heart lies *within the heart itself*, and not within the central nervous system."

The italicized words represent precisely the factor of the problem which must be eliminated to enable us to differentiate the rôle of the coronary plasma from that of the Thebesian plasma, for blood will not alone induce contraction of the cardiac walls; almost any irritant will under appropriate conditions. Indeed, in the latter case it will sometimes undergo contractions without any external irritation; thus, "a strip of muscle cut from the *apex* of the tortoise ventricle and suspended in a moist chamber begins in a few hours to beat apparently of its own accord with a regular, but slow, rhythm, which has been seen to continue as long as thirty hours. If the strip is cut into pieces and placed on moistened glass slides, each piece will contract rhythmically. Yet in the apex of the heart no nerve-cells have been found" (Porter). Hence the power to contract is inherent in the contractile tissues, and subject, as elsewhere in the organism, to exacerbations of activity under appropriate stimulus. This fact being now established, our inquiry is simplified, since we need only to inquire into the nature of the processes through which it is utilized.

Analysis of the requirements of the right heart soon reveals the fact that the muscle-fibers require the same blood-supply that any muscle of the body does. Indeed, we then realize that the coronary arteries are their only source of oxy-

[16] Porter: Journal of Experimental Medicine, vol. ii, p. 391, 1897.

gen. The venous blood that reaches it through the Thebesian channels has been depleted of this gas by the rest of the organism, and the suprarenal secretion, owing to its marked avidity for it, must, while in transit through the inferior vena cava, have deprived it of the little that might have remained in loose combination. We have reviewed the ultimate distribution of the coronary arteries as given by Berdal. It does not differ from that of other text-books. These generally concur in stating that the larger branches are distributed to the connective tissue between the large fasciculi, and once therein divide into arterioles, which, in turn, subdivide into capillaries that entwine the primary muscle-fasciculi. "The capillaries of the myocardium are very numerous," say Böhm and von Davidoff, "and so closely placed around the muscle-bundles that each muscular fiber comes in contact with one or more capillaries." Do they serve here, as elsewhere, to supply the muscle-fiber with its *source of energy—i.e.*, the carbohydrates that enter into the formation of the myosinogen—besides furnishing the oxidizing substance which sustains the combustion processes when brought into contact with this myosinogen? This is precisely where a difference between the muscular functions of the heart and those of other muscular structures appears to us to exist.

There is practically no *passive* period in the heart's action when we consider that its stage of *activity* recurs every three-fourths of a second; and the formation of myosinogen in its contractile elements, were it to proceed as slowly as it does elsewhere, would seem totally inadequate. Still, if the coronary blood is not endowed with the mission of supplying the heart-muscle with its source of energy, we are relegated to the venous blood of the Thebesian vessels and its suprarenal secretion for the myosinogen-forming products. A possible source of energy suggests itself when we consider that a carbohydrate known to react under the effects of the oxidizing substance is present in the hepatic veins,—*i.e.*, dextrose,—and that this sugar must pass through the right heart. As is well known, these veins carry their sugar to the inferior vena cava. That it is not used by the heart, however, was shown by a careful analysis of the whole question. This is submitted in the twelfth

MECHANISM OF CARDIAC ACTION. [Plate]

1, Inferior Vena Cava, the blood of which contains Adrenal Secretion. 2, Hepatic Veins, the blood of which contains granules β derived from the Liver. 3, Right Auricle. 4, One of the Coronary Arteries. 5, One of the Coronary Veins. 6, One of the Foramina Thebesii.

chapter. Paradoxical as the statement may seem, we were led to conclude that the minute granules referred to on page 433 were actually supplied to the heart through the intermediary of leucocytes. These cells were found to migrate from the liver (also through the hepatic veins) to the inferior vena cava, where they meet the adrenal secretion and proceed with it to the right ventricle. The evidence seems incontrovertible. The subject is so far-reaching, however, that it had to be considered separately. We will, for the present only, refer to these granules as "granules β" (Ehrlich). We now have, it seems to us, the elements necessary to account for the functional phenomena witnessed, namely:—

1. The adrenal secretion, to contract the right auricle and ventricle and thus insure the penetration of the Thebesian blood into the cardiac walls (which contraction venous blood or its contained granules β would not cause).

2. The granules β, to account for the unusual and continuous production of energy which the heart converts into work.

3. A continuous supply of oxidizing substance via the coronary arteries to insure the combustion processes through which this energy is liberated.

The annexed colored plate shows the manner in which the adrenal secretion and the granules β simultaneously reach the right auricle.

We can now understand why plugging of the coronary arteries should, as stated by Porter, arrest cardiac action. Referring to the effects of embolism and thrombosis of these arteries, this investigator also says: "That part of the heart-wall supplied by the stopped artery speedily decays. The *bloodless area* is of a dull-white color, often faintly tinged with yellow; rarely it is red, being stained by *hæmoglobin* from the neighboring capillaries. The cross-section is *coarsely granular.* The nuclei of the muscle-cells have lost their power of staining. The muscle-cells are dead, and connective tissue soon replaces them. This loss of function and rapid decay of cardiac tissue would not take place did anastomosis permit the establishment of collateral circulation between the artery going to the part and neighboring arteries. . . . The objection that one of the coronary arteries can be injected from another, and that,

therefore, they are not terminal, is based on the incorrect premise that terminal arteries cannot be thus injected, and has no weight against the positive evidence of the complete failure of nutrition following closure." As we interpret the process, the absence of anastomosis further suggests the existence of an additional source of energy; but the cardiac arrest after ligation of the coronary also indicates that compensation from the opposite heart can only be gradually established. On the whole, the coronaries of the right side are as important as if they alone supplied the needs of the functions of that side. The granules β and the adrenal secretion are furnished to compensate for the absence of *arterial* blood in the right auriculo-ventricular cavities and in their Thebesian channels; but, the right coronaries being the only source of one of the three *necessary* factors of the process, their obliteration means as much as that of the left coronaries does to the left heart.

We can also understand why the contractile elements of the primary fasciculi are bare. They are constantly bathed in the plasma from which they obtain the granules β that enter into the formation of their myosinogen. The absence of oxygen in this fluid renders it perfectly harmless to the delicate structures that surround the primary and secondary bundles of muscle-fiber, and to the net-works of arterial capillaries that hug the bare fibers. The latter, by a rapid absorption,—which the presence of sarcolemma would counteract,—are constantly forming their products of metabolism: *i.e.*, myosinogen. The arterial capillaries, "coated, on their external surface, with flat connective-tissue cells" (Berdal), when they cross the spaces of Henle, being the only carriers of oxygen, normally become the active factors of nutrition and function. Their blood is the normal excitant—as elsewhere. The venous blood brings the granules β; the adrenal secretion, by contracting the cardiac walls, forces it into the Thebesian channels; the bare muscle-fibers absorb the granules and convert them into their own particular kind of fuel, myosinogen; the capillary blood supplies the energy for this metabolism—oxygen—and simultaneously sustains, again with its oxygen, the combustion processes upon which the continuous work of the organ depends. Here, as elsewhere, the potential energy of

the chemical agencies present becomes converted into mechanical energy, which manifests itself as visible motion.

The left heart—the coronaries of which are larger than those of the right—presents anatomical features which modify, in a measure, the manner in which its physiological functions are performed. Both its auricle and ventricle containing arterial blood fresh from the heart, the Thebesian circulation does not appear to fulfill the primary rôle it does in the right heart. Indeed, the various experiments of Pratt and his predecessors and our own careful examination of the ox-heart distinctly show that the Thebesian circulation of the left heart, as regards intraventricular orifices, is much less important than that of the right heart. Still, the evident permeability of the interventricular septum and the histology of the left myocardium suggest that the left heart must receive material aid from the adrenal secretion and its granules β. This feature will again be referred to in the twelfth chapter.

A feature that may be considered as demonstrated, and common to both sides, is the return of the blood, whether its source be the Thebesian or coronary systems, by way of the coronary veins. We have seen that Langer expressed the opinion "that the foramina Thebesii in the ventricles communicate with the veins by capillaries alone." Our conception of the process involved would necessitate such an arrangement as regards the right heart. Indeed, so direct is this connection that even such viscid substances as starch and celloidin were found by Pratt, when introduced into the coronary veins of the ox, to emerge from the foramina Thebesii. Still, we could hardly expect such a free transit on the left side of the organ, inasmuch as the presence here of arterial blood only would suggest the presence of a structural organization similar to that of ordinary muscles. Indeed, referring to the vascular connections of the left heart, Pratt says: "So intimate a connection, however, between the coronary veins and the vessels entering the left ventricle I have not yet been able to demonstrate." Again, on the right side the connection with coronary veins must evidently be a physiological one, since "a small, but steady, stream of venous blood issued from them" when the veins were incised after the right ventricle had been filled with defibrinated blood.

But "no flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein" in an experiment similar to that previously referred to, also performed by Dr. Pratt. In fact, it appears to us very doubtful whether even the capillary communication between coronary arteries and the Thebesian vessels, referred to by the latter observer in his conclusions, at all exists—at least in the walls of the right heart. Even disregarding our views, it seems evident that the admixture of venous blood with the arterial blood would greatly reduce and perhaps annul the functional efficacy of the latter as an oxidizing agent.

We can now understand how the adrenal secretion so greatly influences cardiac activity. An increase of it augments the force of the contraction, but the heart does not dilate as promptly nor perhaps as completely; hence its action is slower, but more forcible; we have seen that this represents the primary effect of all drugs sufficiently active to stimulate the adrenals. A still greater quantity of adrenal secretion increases the violence of cardiac action; the vessels are tense, and ecchymoses, hæmaturia, epistaxis, etc., may ensue. The heart acts normally, however, in the sense that its diastole is almost complete. Continuous cardiac stimulation through excessive production of adrenal secretion, due in turn to excessive production of iodothyrin, as in exophthalmic goiter, causes the heart to contract before it has exhausted its complete diastole and to work within a narrower field. Its contractions are sharp, but rapid: the type of the "cramped heart." Increase of adrenal activity involves increase of oxidizing substance; hence the left heart is correspondingly stimulated. When, however, adrenal insufficiency occurs, the phenomena follow an opposite course; when total inhibition of the adrenal system ensues, the vascular walls, losing all their functional stimuli,—the adrenal secretion, the granules β, and the oxidizing substance,—gradually cease their contractions and lapse into diastole.

THE INNERVATION OF THE HEART.

We are again brought, by analysis, to the realization that the afferent nerves distributed to the heart *incite* and *govern* functional activity but contribute nothing to the continuation

of vital processes *per se*. Indeed, in the heart they do naught else than in other parts of the organism. The general motor system (sympathetic) insures the tonic contraction of the coronaries and smaller vessels; the vagus, when need be, assumes control, to increase or reduce the rapidity of the organ's contractions. "The rich nervous supply of the heart is derived from the coronary *plexuses*," says Piersol, "and *includes* numerous medullated fibers coming from the *pneumogastric* as well as the non-medullated *sympathetic* fibers proceeding from the cervical ganglia. Numerous microscopical ganglia are found along the course of the large nerve-trunks accompanying the branches of the coronary arteries, especially in the longitudinal interventricular and in the auriculo-ventricular furrows. Many additional small groups of ganglion-cells occur within the muscular tissue associated with the fibers supplying the intimate structure."

The similarity between the innervation of the heart and that of the organs of the digestive tract is recalled in the above quotation by the conjoined sympathetic and vagus plexuses, which form around the coronaries what we have termed the "extrinsic" nerves: *i.e.*, those that regulate the amount of blood admitted into an organ. The analogy further asserts itself when the distribution of the terminal fibers, as depicted by Langerhans and Ranvier, is reviewed. Berdal refers to this feature of the terminal supply as follows: "The nerve-fibers which penetrate the depths of the cardiac muscle form, on the surface of the fasciculi, a long-meshed plexus which sends into the interior of these fasciculi still finer fibers. These fibers form a second net-work, the elongated meshes of which present the dimensions of a muscular fiber; but, instead of containing the muscle-fibers in their meshes, the latter seem to traverse them longitudinally."

We can, therefore, base our deductions, as regards the functions of the terminal subdivisions of the sympathetic and vagus nerves in the heart-muscle, upon the analogy which the functions of these nerves in other organs suggest. Their similar distribution, extrinsic and intrinsic, in all the organs that they jointly supply, including the heart, seems to us to afford considerable likelihood that their rôle is similar in the latter organ

to that fulfilled by them in all others. Indeed, it is difficult to conceive of a mechanism in which vasoconstriction and the adjustment of functional activity to requirements could be dispensed with. These factors, in addition to the normal attributes of the afferent fibers of the vagus,—*i.e.*, to transmit to the vagal center impulses that will bring about reflexly the required modification of functional activity,—constitute a simple, though perfect, mechanism, when applied to the phenomena witnessed. They satisfy equally well the needs of the functional activities of the heart-muscle, when supplemented with the all-important adrenal secretion of the Thebesian circulatory system.

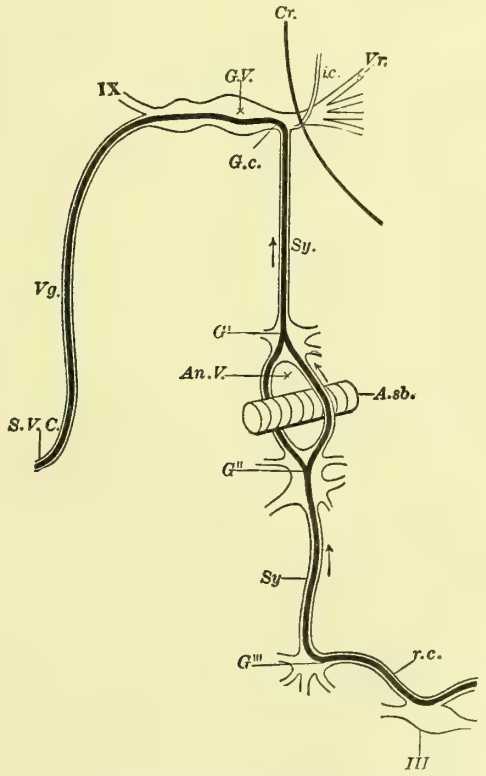
There are two features of cardiac functions connected with the nervous system, however, which appear to us to require interpretations other than those that have been generally accepted: *i.e.*, the "augmentor," or "accelerator," and the "inhibitor" phenomena.

"Augmentor," or "Accelerator," Phenomena.—These consist of an increase of the rapidity of the heart-beats and the force of the beat, "the diastole being shortened and the systole strengthened": the type of cardiac action we have termed, when exaggerated as it is in exophthalmic goiter, the "cramped heart." In reviewing another subject Professor Foster says: "If we stimulate the *sympathetic* in the neck,[17] cutting the nerve below, so as to block all impulses from passing downward, and only allow impulses to pass up to the vagus and thence down the mixed vagus trunk to the heart, we get very remarkable results. The beat of the heart, instead of being inhibited, is *augmented;* the beats are increased, either in frequency or in force, or most generally both in frequency and in force. The effect is, perhaps, best seen when the heart before stimulation is beating slowly and feebly; upon stimulation of the *cervical sympathetic* the beats at once improve in vigor and frequency; indeed, a heart which, for one reason or another, has almost ceased to beat may, by proper stimulation of the sympathetic, be called back into vigorous activity." That we are dealing here with stimulation of the adrenals seems probable.

Indeed, we have added a factor of marked importance to those usually taken into consideration,—*i.e.*, the anterior pitui-

[17] All italics are our own.

tary body,—which becomes itself activated, under these circumstances, through the carotid plexus. The vagus is not alone stimulated, therefore, but the suprarenal glands likewise: precisely the most effective means to bring about the effects witnessed,—as we view the process. This is affirmed by the following remarks by the same author: "Last, the contrast is



DIAGRAMMATIC REPRESENTATION OF THE COURSE OF CARDIAC AUGMENTOR FIBERS IN THE FROG. (*Foster.*)

completed by the fact that the augmentation resulting from the stimulation of the sympathetic is followed by *a period of reaction* in which the beats are feebler; in other words, *augmentation is followed by exhaustion;* and, indeed, by repeated stimulation of these sympathetic fibers, a fairly vigorous bloodless heart may be reduced to a very feeble condition."

Again, the distribution of the nerve clearly points to the adrenals as the source of the "augmentor phenomena." Professor Foster states that it "may be traced from the spinal cord by the anterior root of the third spinal nerve, through the ramus communicans to the corresponding *splanchnic* ganglion *(G''')*, and thence by the second ganglion *(G'')*, the annulus of Vieussens, and the ganglion *(G')* to the cervical *sympathetic (Sy)*, and so by the *vagus* trunk to the superior vena cava *(S. V. C.)*." Indeed, he so accurately traces out, in the annexed illustration, what to us appears to be the direct pathway *to the adrenals*, in the frog, that his own words will serve our purpose: "By watching the effects of stimulating the sympathetic nerve at various points of its course we may trace these augmentor fibers from their junction with the vagus down the short sympathetic of the neck, through the first splanchnic or sympathetic ganglion connected with the first spinal nerve *(G')*, through one or both the loops of the annulus of Vieussens, *(An. V.)*, through the second ganglion connected with the spinal nerve *(G'')*, to the third ganglion connected with the spinal nerve *(G''')*, and thence through the ramus communicans, or visceral branch of that ganglion *(r. c.)*, to the third spinal nerve *(III)*, by the anterior root of which they reach the spinal cord." If, in the illustration, as above described, the identity of *G'''* is noted,—*i.e.*, the *splanchnic ganglion*,—the fact that the "augmentor" stimuli follow the course outlined, to the adrenals, will appear. We have already witnessed the effects of lesions of the bulb in causing overactivity of the adrenals through this nervous path. Especially is it well illustrated by Claude Bernard's memorable experiment, during which he discovered that puncture of the fourth ventricle gave rise to glycosuria: a condition due, we have seen, to suprarenal overactivity.

We must not lose sight of the fact, however, that "augmentor" phenomena do not only include increase of the force of the heart,—attributable, in our opinion, to the adrenal secretion,—but also increase of the rapidity of the heart-beats. It is evident that if the adrenals were the only sources of energy involved in the process we would obtain increased force and *slowing* of the heart's action. To what, therefore, can we

ascribe the quickening of the heart-beats to which stimulation of the augmentor fibers give rise? The answer is easily found in the fact that the vagus fulfills in the heart the same functions it does in other organs: *i.e.*, it *incites* and *governs* the *active* stage of its functional processes. Its prerogatives as governing agency obviously include quickening, as well as slowing, of the heart-beats, the former being the result, as previously stated, of a more rapid vibratory rhythm, while the slowing results from a slower rhythm of the impulses transmitted from the vagal centers. When, therefore, stimulation of the adrenals is induced through the augmentor fibers, the vagal centers are correspondingly stimulated,—owing to the unusual activity of the oxidation processes which the increase of oxidizing substance in the blood engenders,—and the frequency of the heart-beats is augmented in proportion. While the adrenal secretion therefore increases the power of the cardiac pulsations, the vagus increases their number.

We wish to particularly emphasize this combined action of the adrenals and the vagus, since it represents the functional mechanism that underlies the production of fever.

That the first effect of stimulation of the augmentor fibers is produced upon the adrenals, the vagal effects being secondary, is strikingly emphasized by the following remark of Professor Foster's in reference to "augmentor" phenomena: "In contrast with the case of the vagus fibers, a somewhat stronger stimulation is required to produce an effect; the time required for the maximum effect to be produced is also *remarkably long.*"

On the whole, it seems to us quite evident that *stimulation of the "augmentor" fibers increases the rapidity and the force of the heart-beat by increasing the functional activity of the adrenals and, as a result of the increased oxidation processes thus obtained, that of the vagal centers. The excess of adrenal secretion increases the force of the heart-beats, while the overactivity of the vagal centers increases their number.*

"Inhibitor" Phenomena. — We have previously stated that we had not found, in the course of the inquiry to which this work is devoted, the need of a subsidiary function such as that generally understood by the word "inhibition": *i.e.*, arrest, partial or total (by a direct action upon tissues or by interfer-

ence with other nerve-impulses), of the functional activity of an organ. Indeed, direct "inhibition" does not appear to us to prevail in the organism any more than does direct "vaso-dilation." Nor do we find the need of such an action to account for the "inhibition" phenomena witnessed in connection with the heart—provided, of course, the functions we ascribe to the vagus are considered as factors of the process through which this organ is inhibited. It seems evident to us that, if this nerve can quicken or moderate the pace of the cardiac contractions, arrest of these contractions must ensue if the impulses transmitted through the nerve exceed in vibratory rhythm the maximum rhythm of which the heart-muscle is capable. In other words, there must obviously be a limit to the speed with which the cardiac muscle can repeat its contractions within a given time, and, excessive stimulation involving a greater number of heart-beats than the muscle can satisfy, cessation of the organ's work normally follows.

"If while the beats of the heart of a frog are being carefully registered," says Professor Foster, "an interrupted current of moderate strength be sent through one of the vagi, the heart is seen to stop beating. It remains for a time *in diastole* perfectly motionless and flaccid; all the muscular fibers of the several chambers are, for the time being, in a state of relaxation. The heart has been *inhibited* . . ." The overwhelming importance of this simple experiment becomes emphasized when the influence of excessive suprarenal activity upon the oxidation processes of the vagal centers, to which we have just referred, are given their full meaning. Indeed, the *cardiac arrest that follows overstimulation of the adrenals under the influence of toxics is due to excessive activity of the oxidation processes in a certain proportion of cases.*[18]

Whether cardiac inhibition be due to cessation of suprarenal functions or to excessive vagal stimulation, the effect on the heart is the same as regards the mode of arrest: *i.e.*, in diastole. We have just seen that it occurs in the frog when the vagus is stimulated. We have also submitted evidence to

[18] As such cases are clearly defined,—as we shall see in a subsequent chapter,—their importance lies in their differentiation from cases in which the adrenals are primarily arrested through excessive stimulation of their center: the anterior pituitary body.

show that diastole was the type of cardiac arrest that followed total suprarenal inhibition due to overstimulation. Even digitalis will arrest the heart in diastole.[19] Arsenic, chloral, atropine, the bromides, aconite, hyoscyamus, creosote, guaiacol, antipyrin, acetanilid, iodoform—are types of the active drugs used in practice which, when administered in adequate doses, do what the current does through the vagus: *i.e.*, inhibit the heart. Even quinine, one of the safest suprarenal stimulants, is capable of causing heart inhibition. "The evidence is conclusive," says Wood, "that both in man and in the lower animals quinine in sufficient amount is a powerful depressant to the heart-muscle and ganglia."

"Both Schroff and Jerusalimsky noticed that the fall of arterial pressure produced by quinine," continues Professor Wood, "is *preceded* by a rise of pressure accompanied by an increase of the cardiac action. This observation has been confirmed by G. Sée and Bochefontaine; but no observer seems to have shown that the rise of pressure is more than a temporary phenomenon." The kinship with vagal overstimulation and the fact that it is but temporary are clearly defined in this sentence.

The parallelism between excessive vagal action and the action of drugs on the adrenals is further exemplified in the following sentence of Professor Foster's: "With a current of even *moderate* intensity—such a current, for instance, as would produce a marked tetanus of a muscle-nerve preparation—the stand-still is complete,—that is to say, a certain number of beats are entirely dropped; but with a *weak* current the inhibition is *partial only:* the heart does not stand absolutely still, but the beats are slowed, the intervals between them being prolonged, or weakened only without much slowing, or both slowed and weakened. Sometimes the slowing and sometimes the weakening is the more conspicuous result." We have here, again, the expression of the functional activity of both the vagus and the suprarenal glands—with fluctuations in their individual supremacy. This is further illustrated by the following experimental data: "It sometimes happens," says Professor Foster, "that, when in the frog the vagus is stimulated

[19] H. C. Wood: *Loc. cit.*, 297.

in the neck, the effect is very different from that just described, for the beats are increased in frequency, though they may at first be diminished in force. And, occasionally, the beats are increased both in force and frequency; the result is augmentation, not inhibition."

This suggests that confusion must inevitably reign when it becomes necessary to clinically determine the meaning of danger-signals, but if the tendency of the adrenals to *strengthen* and *reduce* the pulse-rate, while that of the vagus—under excessive oxidation—is to *quicken* it, is borne in mind, and, furthermore, that *weakness* of the heart-stroke portrays corresponding weakness of suprarenal activity, no confusion need exist. Of course, all this rests upon our assertion that oxidation processes when enhanced by overactivity of the adrenals correspondingly increase the heart-beats. That such is the case may be illustrated by the following sentence of Professor Wood's in his section on the physiological action of quinine: "Jerusalimsky attributes the increase of the pulse-rate to paralysis of the inhibitory apparatus: a view which is supported by the assertion of Cerna that previous section of the pneumogastric *prevents* the quickening of the pulse-rate." Our interpretation of the functions of the vagus does not, of course, harmonize with the words "paralysis of the inhibitory apparatus," since a far less complicated process—inordinate activity of the vagal functions—accounts, according to our view, for the occurrence of inhibition. Furthermore, we look upon this phenomenon as pathological and absolutely removed from the physiological purposes that the words "inhibitory apparatus" imply: a feature which necessarily emphasizes our belief that no such apparatus exists. Briefly, the phenomenon generally recognized under the term "inhibition" appears to us to be accounted for in the following deductions:—

1. No cardiac inhibitory apparatus exists as a physiological entity.

2. Active inhibition of the heart may be caused by excessive stimulation of the vagus.

3. Passive inhibition of the heart is primarily due to insufficiency of the adrenals.

The reasons for this are embodied in the following general

summary of the functional mechanism of the heart as developed in the present chapter:—

1. The nervous supply of the heart is derived from the general motor (sympathetic) and vagus systems.

2. The general motor plexuses and nerves maintain the normal tonic contraction of the coronaries and other cardiac vessels and insure distribution of the blood among the muscular elements.

3. The vagal plexuses and nerves incite and govern the rhythm of the heart, reducing or increasing its beats.

4. Increase of the vagal vibratory rhythm (impulses) causes quickening of the heart-beats.

5. Excessive vibratory rhythm of the vagus (or spinal accessory) causes arrest of the heart-beats: i.e., inhibition.

6. Reduction of the vagal vibratory rhythm causes, when physiological, slowing of the heart-beats.

7. Reduction of the vagal vibratory rhythm, when pathological, especially when due to adrenal insufficiency, results in quickening and weakening of the heart-beats, through loss of vagal control.

8. Cessation of the vagal vibratory rhythm (as after division of the vagus on both sides) is followed by marked quickening and weakening of the heart-beats, through loss of vagal control.

9. The mechanical energy upon which the right heart depends is of two kinds: (1) the contractile action of the adrenal secretion brought to it by the inferior vena cava; (2) the continuous action of the oxidizing substance of the coronary arterial blood upon myosinogen formed from granules β, the latter being derived from the liver.

10. The adrenal secretion and the granules β enter the right auricle and the right ventricle with the blood of the vena cava.

11. The adrenal secretion, owing to its direct action on muscular tissue, causes the walls of these cavities to contract alternately upon their venous contents and to force a small quantity of the latter into the Thebesian foramina and channels.

12. This blood then penetrates the interfibrillary spaces of Henle,—i.e., around the bare muscle-cells,—and its granules β are used by the latter to build up their myosinogen.

13. As the plasma of the coronary arteries and their terminals, the pericellular capillaries of the muscle-elements, contain oxidizing

substance, contraction of the muscle-cells is induced as it is elsewhere in the organism.

14. The adrenal secretion and the granules β, which do not enter the Thebesian channels, are carried to the lungs with the venous blood of the right ventricle.

15. The mechanical energy of the left heart is supplied (1) by the oxidizing substance of the arterial blood, which penetrates its muscular structures and its cavities by the coronaries and the pulmonary veins, and (2) by an additional supply of myosinogen-building granules β, and perhaps of adrenal secretion, which find their way to its myocardium through the Thebesian channels that connect it with the right heart.

16. The manner in which the contractile process is carried on in the walls of the left heart is similar to that which prevails in the right heart.

THE ADRENAL AND VAGAL SYSTEMS IN THEIR RELATIONS TO RESPIRATORY FUNCTIONS.

The rôle of the suprarenal secretion in respiration, and particularly the process through which oxygen is taken up by the blood, was reviewed in the second chapter. We believe that the succeeding chapters, by affirming the importance of the oxidizing substance in every part of the organism, have but confirmed the conclusions reached concerning the process in question. The fact that the interchange of oxygen and carbonic acid between the alveolar air and the blood by mere diffusion was inadequate to account for the experimental results of various investigators, particularly Bohr and Haldane and Smith, has therefore been correspondingly emphasized. We must also refer to the fact, however, that the belief of Ludwig, Bohr, and others, that the alveolar tissues might be the seat of functions capable of fulfilling the missing requirements of the process, has not been sustained by our inquiry. On the other hand, the rôle of the adrenal secretion in the lungs as we have defined it seems to have supplied these requirements, notwithstanding the severe tests to which it has been submitted in previous chapters.

We have seen that the adrenal secretion, conveyed to the lungs with the venous blood, is not only able to take up oxy-

gen, but to form an oxidizing substance with the latter from which hæmoglobin can, in the lungs, become replenished with oxygen. The entire set of analyses submitted in this work so far, however, seem to us to have emphasized another fact: *i.e.*, that *the plasma, and not the corpuscle, is the dispenser of oxygen,* the corpuscle being a mere carrier from which the plasma itself becomes replenished as needed. As already stated, this precisely coincides with the conclusion to which Jaquet was led by chemical methods (see page 134) after Salkowski (1881) had obtained oxidations from blood alone, which he attributed, however, to the blood-corpuscles. Abelous and Biarnés having obtained oxidation of salicylic aldehyde by means of blood-*serum,* Salkowski modified his former view and experimentally confirmed the results of the other investigators.

Finally, we were able to show how closely connected the suprarenal secretion is with the integrity of the blood, and how readily the hæmoglobin molecule becomes dissociated in proportion as the efficiency of the adrenals becomes weakened. We have traced this dissociation down to the last cleavage-product, hæmatoporphyrin or hæmatoïdin, the coloring pigment in bronzing, which corresponds with the lowest stage of adrenal insufficiency.

The circulatory, nervous, and muscular mechanisms of the lungs are the remaining features to be analyzed.

THE INNERVATION OF THE RESPIRATORY SYSTEM.

THE IDENTITY OF THE RESPIRATORY CENTER.—The absolute independence of the suprarenal system—the adrenals receiving their impulses from the anterior pituitary body—is well illustrated by the following lines by Professor Foster: "Observations show that under particular conditions, and especially in young animals, respiratory movements may be carried out in the entire absence of the medulla oblongata. Thus, if, in a kitten or puppy or young rabbit, after division of the spinal cord below the medulla artificial respiration be kept up, and then pauses be made in the artificial respiration, during these pauses not only may what appear to be respiratory movements be induced in a *reflex manner,* by pinching or by blowing on the skin, but, especially if the excitability of the spinal

cord be heightened by small doses of strychnine, even spontaneous efforts of breathing may occasionally be observed." . . . "Since in such cases the rhythmically repeated movements of the respiratory muscles are sometimes accompanied by rhythmic movements of the fore- and hind- limbs not respiratory in nature, it may be doubted whether these experiments really prove the existence of distinct respiratory centers in the spinal cord." That the data previously given further tend to diminish the likelihood that any such center exists seems obvious.

And still the existence of such a center seems to be sustained by experimental evidence. Thus, division of the cord below the seventh cervical nerve arrests costal respiration; section below the medulla causes all thoracic movements to cease; removal of the brain *above* the medulla, the seat of the supposed center, does not stop respiration, while cessation of this function occurs when the medulla is removed or extensively injured, save in exceptional cases. After reviewing this evidence Professor Foster adds: "Nay, more; if only a small portion of the medulla—a tract whose limits have *not been clearly defined*,[20] but which may be described as lying below the vasomotor center in the immediate neighborhood of the nuclei of the vagus nerves—be removed or injured, respiration ceases, and death at once ensues. Hence this portion of the nervous system was called by Flourens the vital knot, or ganglion of life: *nœud vital*. We shall speak of it as the *respiratory center*."

The first question that suggests itself is the following: Can the respiratory center be a portion of the vagus center, in the immediate neighborhood of which it is generally located? Professor Foster remarks, in this connection: "In attempting to decide this question we naturally turn to the pneumogastric as being the nerve most likely to serve as the channel of afferent impulses setting in action the respiratory center. If both vagus nerves be divided, respiration *still continues*, though in a *modified* form.[21] This proves distinctly that afferent impulses ascending those nerves are not the efficient cause of the

[20] The italics are our own.

[21] All italics are our own.

respiratory movements." . . . "One cranial nerve, as we shall see, is especially concerned in respiration, viz.: the vagus nerve; but if, after removal of the brain above the medulla, both vagus nerves be divided, respiration *still goes on;* indeed, the respiratory impulses proceeding from the center are, though in a peculiar way, exaggerated." A feature of the experiments referred to is that electricity is not in any way stated to have been used; we are dealing, therefore, with positive facts, which may be summed up in the statement that *division of the vagus does not arrest respiration.* Such being the case, how can the vagal center be considered as the respiratory center, or as Flourens's *nœud vital?* If removal or injury to the latter suffice to arrest respiration, section of the vagi should do the same. Since it does not, it seems obvious that the respiratory center cannot be vagal, and that the "*nœud vital*" is not the respiratory center.

The rôle of the vagus in pulmonary functions becomes clear, however, if we grant this nerve functions similar to those we have found it to fulfill elsewhere: *i.e.*, as companion to the general motor nerves, and intended to incite and govern the exacerbations of functional activity assumed when from "passive" the organ's work becomes "active," and to transmit to the bulb the impulses that bring on the counter-impulses which maintain and regulate—temporarily and in lieu of its mate, the general motor supply—these exacerbations of activity. It might well be severed under these circumstances without arresting respiration. The general motor fibers would merely continue their work, though "in a peculiar, exaggerated" way.

If the vagal center is not that which presides over respiration, to which portion of the bulb can we ascribe this important function. With our limited array of nervous systems to choose from, we are led to consider the "general motor center" *in toto* as a respiratory center. But a curious fact appears when this question is closely studied: *i.e.*, that what has been called the "respiratory center" includes the parts of the bulb which we consider as the "general motor center" and "the vasomotor center," or rather the area to which the latter term has been applied.

"The portion of the medulla the removal of which exerts

an influence on the blood-pressure, according to Owsjannikow, extends from a point 4 to 5 millimeters above the *point* of the calamus scriptorius to within 1 to 2 millimeters of the corpora quadrigemina," says Professor Stewart,[22] who also remarks that other observers give narrower limits, and adds: "Stimulation of the medulla causes a rise, destruction of this portion of it a fall, of general blood-pressure. There is evidently in this region a nervous center so intimately related, if not to all the vasomotor nerves, at least to such very important tracts as to deserve the name of vasomotor center. Experiment has shown that it is much the most influential center, and it is usually called the chief, or general, vasomotor center. But there are subsidiary centers all along the cord, and, while a very large number of the constrictor fibers are related to the chief center of the medulla, some are either normally under the control of subordinate centers or may in special circumstances come to be dominated by them." If the floor of the fourth ventricle is examined, the area comprised between "a point 4 to 5 millimeters above the point of the calamus scriptorius to within 1 to 2 of the corpora quadrigemina" will be found to include practically all the bulbar nerve-centers, so that the "vasomotor center" may be said to include the bulbar origin of practically all nerves.

Again, it is manifest that the term "vasomotor" applies to nerves distributed to vessels throughout the entire organism: *i.e.*, wherever terminal arterioles occur. If we now recall our view that each general motor nerve distributed to a part supplies it with its vasomotor fibers as well as with all others distributed to it,—unless associated with a special nerve, such as the vagus,—the deduction imposes itself upon us that the vasomotor center in the medulla must coincidently be that of the general motor nerves or at least the region where the latter assume vasomotor functions.

Even reducing the area represented by the vasomotor "center" to the narrowest limits recognized by physiologists, it may conservatively be said to include at least one-half of the fourth ventricle. If we now ascertain the nerves involved in this area, the suggestive fact asserts itself that this upper half

[22] Stewart: *Loc. cit.*, p. 158.

contains *all* nerves that possess motor properties. The following list of the seven cranial nerves in the upper half of the medulla will illustrate the relationship:—

1st pair. Olfactory: *No* motor function; no bulbar connection.

2d pair. Optic: Filaments from 3d pair for iris and ciliary *muscles.*

3d pair. Motor oculi: Filaments from *corpora quadrigemina;* supplies collateral fibers to ophthalmic ganglion for iris and ciliary *muscles.*

4th pair. Patheticus: Fibers terminate in *corpora quadrigemina;* supplies fibers that govern superior oblique *muscle.*

5th pair. Trigeminal: Upper part of floor and anterior wall of fourth ventricle. Small root of masticatory *muscles.*

6th pair. Abducens: Upper part of floor of fourth ventricle; supplies external rectus *muscle.*

7th pair. Facial: Upper part of floor of fourth ventricle; supplies levator palati, azygos uvulæ, tensor tympani, stapedius, and the external *muscles* of the ear, face, etc.

Again, all nerves that anastomose with *motor* fibers or require them in addition to their own are in some way connected with the fourth ventricle:—

9th pair. Glossopharyngeal: Lower part of fourth ventricle. Supplies palatal and pharyngeal *muscles,* through anastomosis.

10th pair. Pneumogastric: Lower part of fourth ventricle. Supplies œsophageal, cardiac, gastric, etc., *muscles,* through anastomosis.

11th pair. Spinal accessory: Lower part of fourth ventricle and cord. Supplies laryngeal, deglutitory, cardiac, and respiratory *muscles.*

12th pair. Hypoglossal: Lowest portion of fourth ventricle. Supplies lingual, masticatory, deglutitory, etc., *muscles.*

Still these only represent the motor nerves or motor anastomoses. The *vaso*motor connections are not referred to; but, inasmuch as the vasomotor center has been experimentally shown to be located in the medulla, it now behooves us to account for the presence, *besides* the motor nerves just referred

to, of "sympathetic" fibers in some organs. Having totally disconnected the suprarenal system (the thyroid, the anterior pituitary, the splanchnics, and the adrenals) from the vasomotor system, the latter, viewed from our standpoint, merely represents subdivisions of the general motor system at all times. We are, therefore, bound to point to a vasomotor function as an attribute of all motor nerves. Of course, the vasomotor center being admittedly located in the fourth ventricle and the table just submitted showing that all motor nerves or motor connections are related with the same structure, a step in the elucidation of this point has been made; but we have still to complete the list by showing that even these apparently independent filaments also arise from the medulla or cord.

The nerves that receive filaments from the sympathetic are the 3d, 4th, 5th, 6th, 10th, and 12th. The 3d, or motor oculi, which supplies several eye-muscles, the circular fibers of the iris, and the ciliary muscle, receives its sympathetic filament from the cavernous plexus. The latter can only be derived in this locality from one of two sources: either the suprarenal system nervous connections or the spinal cord through cervical or dorsal nerves (unless conjoined with the vagal or glosso-pharyngeal roots, which is unlikely). Pupil-dilating fibers were traced by Sherrington, in monkeys, and by Langley, in cats and dogs, in the first and second and to a less extent in the third and fourth dorsal nerves. Onuf and Collins[23] refer to the observations of Müller in the case of "a man in whom a lesion could be distinctly located in the region of the first and second dorsal nerve-roots, and in this case there was marked contraction of the pupil, ptosis, and sinking in of the eyeball." They state that the results of investigators indicate that the pupil-dilating fibers occur with the greatest constancy in the first dorsal and almost constantly in the second dorsal, and refer to the fact that Salkowski placed the origin of these fibers *in the medulla oblongata.* Finally they express the opinion that, "although the evidence is *preponderatingly in favor* of the existence of a *cilio-spinal* center, yet the question has not been definitely settled."

The *fourth* pair, or patheticus, which governs the action

[23] Onuf and Collins: *Loc. cit.*, p. 90.

of the superior oblique muscle, also receives filaments from the cavernous plexus of the sympathetic; hence its connection with the medulla through dorsal nerves is as likely as in the case of the third nerve. The *fifth* pair, or trigeminal, receives its sympathetic filaments from the carotid plexus: that connected with the anterior pituitary lobe. Examination of this communication, however, shows that the cavernous plexus is the nearer one, and that the connections with it are direct by two decussating embranchments. Though there would be no difference as to its functional isolation and its probable connection with the medulla,—except if electricity be used,—were its fibers conjoined to those of the carotid plexus (different nerves often following the same path), it is probable that the sympathetic filaments to the third pair are connected with the cavernous plexus, and that they are also, therefore, of medullary origin. The *sixth*, or abducens, is also stated to receive its sympathetic filaments from the carotid plexus through the Vidian, but again is it found on examination that the Vidian is connected, not with the carotid plexus, but primarily through a branch which in turn decussates from the main trunk,—the so-called superior ganglion of the sympathetic,—from which also originates the cavernous plexus. The *twelfth*, or hypoglossal, receives its sympathetic branch from a spot below this and evidently from the same trunk. Hence the 4th, 5th, 6th, and 12th may be said to be traceable to a common—and adjoining—source through the original source of the cavernous plexus: *i.e.*, the cord. Finally the *tenth*, or pneumogastric, receives the three cardiac "sympathetic" nerves, which contribute to the formation of the cardiac plexus. The origin of these nerves and their motor functions we have already reviewed.

All these facts seem to us to completely establish the general motor system as a functional entity, and to centralize in the medulla and the cord all the sources of functional *motor* activity that depend upon nervous impulses. Inasmuch as it includes within its manifestations of activity all vasomotor functions, it seems clear to us that to remove or destroy this vasomotor area means simply to remove or destroy—what we may call for the time being—the centers of functional activity

of the medulla and upper cord. Still, we have seen that the vagus cannot be considered as the respiratory center; what then is there in the medulla that can be termed such? A moment's reflection will now suggest that there is no such a center as the respiratory center, and that the morbid phenomena witnessed after section of the medulla are really due to interruption of the *general stream* of motor impulses that the bulb serves to transmit. Neither is the general vasodilation that is invariably witnessed after section of the medulla due to interruption of vasomotor impulses *per se.* There is no such a "vasomotor" center; and vasodilation is also due to interruption of the functions of all motor nerves, since it is these which throughout the entire organism maintain tonic contraction of the vessels.

We can further sustain this by analyzing the prevailing view that the "respiratory center" may be stimulated by the presence of carbonic acid in the blood, and that the vasomotor center is also directly stimulated by a highly venous blood. "When by reason either of any hindrance to the entrance of air into the chest," says Professor Foster, "or other interference with the due interchange between the blood and the pulmonary air or of a greater respiratory activity of the tissues, as during muscular exertion, the blood becomes less arterial, more venous,—*i.e.*, with a smaller charge of oxygen and more heavily laden with carbonic acid,—the respiration, from being normal, becomes labored. We may speak of normal breathing as eupnœa, and say that this, when the blood is insufficiently arterialized, passes into dyspnœa, . . ."

The pathogenesis of dyspnœa was referred to a few pages back. The following lines by the same author will recall some of the features then referred to: "When a muscle contracts, its consumption of oxygen and production of carbonic acid, especially the latter, are increased; the blood leaving the muscle is more venous then usual. Hence, when many muscles are contracting powerfully, the blood carried to the right side of the heart is more venous than usual; and we might expect that it is this unusually venous blood failing to be adequately arterialized in the lungs, and hence reaching *the medulla* from the left side of the heart in a more venous, less completely

arterialized condition than usual, which stirs up the respiratory center to increased activity. On examination, however, it is found that the blood leaving the left side of the heart in such cases is *not the less arterialized*, but, if anything, more arterialized than usual." . . . "Obviously the blood coming from the tetanized muscles affects the respiratory center by virtue of some quality which, unlike that due to the deficiency of oxygen or excess of carbonic acid, is not immediately affected by the passage through the lungs. Whether the quality in question be dependent on an excess of sarcolactic acid, or on some other product or products of muscular metabolism, we do not as yet know." It is very clear, from all this, that it is not the venous blood that reaches the medullary centers which gives rise to the phenomena witnessed, but the products of metabolism themselves, which react upon the *anterior pituitary body*, and through it upon the adrenals, as do other poisons.

Indeed, if we consider the course of events in cases of asphyxia,—the "general convulsions of the whole body, which, however, have to a certain extent an expiratory character," followed by "exhaustion," which "begins to set in," the rhythm becoming "slower than proportionate to the weakening of the individual movements,"—the part played by the suprarenal system affirms itself, combined with and aggravated by the gradual decline of all physiological processes that depend upon proper aeration of the blood. Again, therefore, does the "respiratory center" in the medulla show itself unable to stand analysis. Asphyxia, moreover, is not due, evidently, to the action of CO_2 upon a medullary center; its active symptoms are due to *intoxication by products of metabolism*, while its passive phenomena—air-hunger, cyanosis, etc.—are the result of gradually declining functional activity. On the whole, the following conclusions seem warranted:—

1. There is no individual center in the medulla oblongata to which the term "respiratory center" can be applied.

2. The morbid phenomena witnessed after section of the medulla are due to interruption of the stream of general motor impulses which the medulla serves to transmit.

3. There is no individual center in the medulla oblongata to which the term "vasomotor center" can be applied.

4. The general vasodilation witnessed after section of the medulla is due to the interruption of the stream of general motor impulses through which tonic contraction of the arteries is maintained, and which the medulla serves to transmit.

THE INNERVATION OF THE RESPIRATORY MUSCLES.

How, in the absence of a respiratory center, are the respiratory movements governed?

After reviewing the part played by the muscles involved in the respiratory mechanism, Foster says: "It is impossible that all these so carefully co-ordinated muscular contractions should be brought about in any other way than by co-ordinate nervous impulses descending along efferent nerves from a co-ordinating nervous center. By experiment we find this to be the case. When in a rabbit the trunk of a *phrenic* nerve is cut, the diaphragm on that side remains motionless, and respiration goes on without it. When both nerves are cut, the whole diaphragm remains quiescent, though the costal respiration becomes excessively labored."

Even did a "respiratory center" exist, the co-ordinating impulses upon which the diaphragm depends for its rhythmic contractions would not be accounted for unless we grant the phrenic nerve vagal properties: *i.e.*, afferent, as well as efferent, fibers. The origin of this nerve in no way indicates this to be the case. In fact, it appears to us only as a secondary nerve, such as any subdivision of the brachial plexus would be, since it only arises from a branch of the third, fourth, and fifth cervical nerves. Yet this very subdivision seems suggestive, for, if the origin of the phrenic—*i.e.*, its connection with the third cervical—be closely examined, it will be found to meet, or inosculate with, a communicating branch of the *hypoglossal.* This would place the diaphragm on the same plane, as regards nervous supply, as the lungs themselves, since it would then be supplied (1) with general motor fibers, and (2) with hypoglossal fibers which immediately adjoin, in the fourth ventricle, the origin of the vagus. This would fully account for the co-ordination referred to, and which the phrenic as a mere motor nerve would not explain were even a respiratory center present.

The same dual supply should prevail, however, in the external respiratory muscles. "When an intercostal nerve is cut," continues Professor Foster, "no active respiratory movements are seen in the intercostal muscles of the corresponding space, and, when the spinal cord is divided below the origin of the seventh cervical spinal nerve,—that is, below the exits of the roots of the phrenic nerves,—costal respiration ceases, though the diaphragm continues to act, and that with increased vigor." Again is the co-ordinating factor absent. The twelve intercostal nerves are now considered as mere motor nerves and lack afferent fibers capable of accounting for the impulses that call forth counter-co-ordination impulses from the bulb. Each nerve, however, is thought to be accompanied by a filament from the sympathetic—also an efferent nerve—and occasionally (only on the left side, according to Swan) with communicating branches from the hypoglossal. We have not met, as yet, muscles supplied with *two* motor nerves—excepting when the associate nerve was vagal. On the other hand, so important a function as adjustment of the intercostal muscles to corresponding functions would hardly be satisfied by a set of "occasionally present" filaments. We are, therefore, inclined to consider what is now thought to be "sympathetic" filaments as themselves hypoglossal filaments, to which the adventitious ones would stand as anomalous duplications.

Indeed, close examination reveals the following facts: each intercostal *artery* receives a vasomotor filament from the ganglion immediately *above* it, while each intercostal *nerve* receives two thicker branches from the ganglion *below* it. The manner in which the decussations occur and the way in which their distribution is disposed suggest that two nerves, as is the case higher up, are insheathed in each ganglion. Under these circumstances, *hypoglossal* fibers from the medulla would insure the *co-ordinating* attributes to the muscles, in conjunction with the latter's recognized general motor nerves, the intercostals—thus normally accounting for the precision with which the latter fulfill their functions, which otherwise remains unexplained.

That considerable confusion now exists regarding the part taken by ganglionic branches of communication is suggested

by the following quotation from Onuf and Collins's article[24]: "According to Gaskell, most of the motor fibers of the rami communicantes are *cerebro-spinal;* those of the gray rami communicantes, for the most part, sympathetic. *Nothing definite is yet known* concerning the mode of origin of the *sensory fibers* of the sympathetic system nor of the manner of their connection with the cerebro-spinal system. Kölliker claims that all *sensory fibers* of the sympathetic originate from cells of the spinal ganglia in exactly the same manner as the sensory fibers of the cerebro-spinal system."

While a study of the vasomotor functions connected with the sympathetic nerves, as portrayed in the literature based on experimental evidence, distinctly indicates that they invariably transmit efferent impulses, it is evident that *some* fibers supplied by the ganglia *experimentally* furnish afferent impulses,—such as their identity as hypoglossal nerves would involve,—otherwise such authoritative observers as Gaskell and Kölliker could not have referred to them as *sensory* fibers. That the hypoglossal must be the medullary nerve involved is further shown by the fact, referred to by Foster in the last quotation, that section of the cord below the origin of the *phrenic* nerve—which, as we have just shown, is conjoined with the hypoglossal—causes costal respiration to cease. As the hypoglossal, for us, is similar, functionally, to the vagus, the entire *active* nervous supply of these muscles had thus been interrupted.

"When the cord is divided just below the medulla all thoracic movements cease, but the respiratory actions of the nostrils and glottis still continue. These, however, disappear when the facial and recurrent laryngeal nerves are divided." The co-ordinative attributes of the larynx are self-evident, since the recurrent laryngeal is a branch of the vagus; but through what agency are they insured in the case of the nostrils? The facial is a general motor nerve which acquires sensory filaments from the vagus and from the fifth pair. Unless we eliminate the levator anguli oris et alæ nasi from the co-ordinated structures, filaments from the vagus must

[24] Onuf and Collins: *Loc. cit.*, p. 13.

be traced to it, or the nasal branch of the fifth which supplies the levator muscle must be considered as a factor of the co-ordinating system. As the latter's motor and sensory roots are situated in the medulla, there is nothing to militate against its being considered precisely as is the vagus elsewhere. Indeed, we are led, by the strict delineations established between various parts of the organism by the older anatomists, to attach undue importance to names, and the nerve in question may, while being called "trigeminus,"—merely because of its physical attributes,—be an inherent portion of a general system of which other subdivisions called pneumogastric, hypoglossal, etc., may form part.

The fact that "when the cord is divided just below the medulla all thoracic movements cease" implicates all the muscles of the neck and thorax, besides the intercostals, in the co-ordinative process. The usual separation of these muscles into two classes,—one for normal respiratory movements, another for excessive respiratory effort, the latter being brought into action to reinforce the former,—affirms the existence, beyond mere co-ordination, of a function such as we have ascribed to the vagus in various organs. The prevailing views as to the way these muscles take part in the respiratory process give no clue to the manner in which their functions are adjusted to the fluctuating needs of this process, the "respiratory center" being supposed to supply the required impulses when need be.

The relationship we have suggested between the phrenic nerve and the hypoglossal, in the case of the diaphragm, again shows itself in this connection. As is well known, the phrenic nerve is also termed the "internal respiratory" nerve by Bell. If the origin of the "*external* respiratory nerve of Bell" (the posterior thoracic) is examined, it will also be found so related with its mate, particularly at its junction with the fifth cervical, as to clearly indicate a common origin. It is an extensive nerve, and supplies filaments to each digitation of the serratus magnus: a "reinforcement" muscle. That ample communication with the medulla to satisfy the needs of perfect co-ordination exists is further shown by the fact that communications also appear through a vagal branch (first cervical), three hypo-

glossal branches (first, second, and third cervical), and two spinal accessory branches (second and fourth cervical).

Summarized, the innervation of the muscles of respiration appears to us to be as follows:—

1. The nervous supply of the respiratory muscles is composed (1) of divisions of the general motor system, and (2) of divisions of the vagal system.

2. The divisions of the general motor system are (1) the phrenic (the internal respiratory nerve of Bell), distributed to the diaphragm; (2) the intercostals, distributed to the parietes of the thorax and abdomen; and (3) the posterior thoracic (the external respiratory nerve of Bell), distributed to the serrati magni.

3. The divisions of the vagal system are (1) the hypoglossal, distributed to the diaphragm (conjoined to the phrenic) and to the intercostal and external respiratory muscles (instead of sympathetic); (2) the inferior laryngeal, distributed to the muscles of the larynx (except the cricothyroid); and (3) the superior laryngeal, distributed to the cricothyroid muscle.

4. The divisions of the general motor system maintain tonic vascular contraction in, and nutrition of, the respiratory muscles, while the divisions of the vagal system incite and govern their functional and co-ordinative activity.

5. The mechanical energy of the respiratory muscles is the result, as in all muscular tissues, of a chemical action of the oxidizing substance of the blood-plasma upon the myosinogen of the muscle-cells.

THE NERVO-VASCULAR MECHANISM OF THE LUNGS.

The pulmonary circulation as regards general distribution is succinctly portrayed in the following description by Miller,[25] as given by Böhm and von Davidoff[26]: "The *pulmonary artery* follows closely the bronchi through their entire length. An arterial branch enters each lobule of the lung at its apex, in close proximity to the bronchus. After entering the lobule the artery divides quite abruptly, a branch going to each infundibulum; from these branches the small *arterioles* arise which supply the alveoli of the lung. 'On reaching the air-sac

[25] Miller: Journal of Morphology, vol. viii, p. 165, 1893.
[26] Böhm and von Davidoff: *Loc. cit.*

the artery breaks up into small radicles, which pass to the central side of the sac in the sulci *between* the air-cells, and are finally lost in the rich system of capillaries to which they give rise. This net-work surrounds the whole air-sac and communicates freely with that of the surrounding sacs.' This capillary net-work is exceedingly fine, and is shrunken *into* the epithelium of the air-sacs; so that between the epithelium and the capillary there is only the *extremely delicate* basement membrane. The infundibula, the alveolar ducts and their alveoli, and the alveoli of the respiratory bronchioles are supplied with similar *capillary net-works.* The veins collecting the blood from the lobules lie at the periphery of the lobules in the interlobular connective tissue, and are as far distant from the intralobular arteries as possible. These veins unite to form the larger pulmonary veins. The bronchi, both large and small, as well as the bronchioles, derive their blood-supply from the *bronchial arteries,* which also partly supply the lung itself. Capillaries derived from these arteries surround the bronchial system, their caliber varying according to the structure they supply: finer and more closely arranged in the mucous membrane, and coarser in the connective-tissue walls. In the neighborhood of the terminal bronchial tubes the capillary nets anastomose freely with those of the *respiratory* capillary system." To avoid confusion we may recall the fact that, while the *pulmonary* artery and its branches contain *venous* blood, and the *bronchial arteries* and their branches carry *arterial* blood, the pulmonary *veins,* on the contrary, contain *arterial* blood. When, therefore, bronchial capillaries are said to empty into the pulmonary veins, it is not used, or venous, blood that is transferred to the latter, but arterial blood originally derived from the thoracic aorta or its primary branches.

The innervation of the lungs, as in the extrapulmonary respiratory structures, consists of vagal and the general motor nerves. These unite to form plexuses, the anterior and posterior, which enter the organs with the bronchial tubes and accompany them along their ramifications. The anterior pulmonary plexus, made up of vagal and sympathetic filaments, overlies the pulmonary artery, while the richer posterior pulmonary plexus, composed also of vagal filaments, intermixed with sympathetic

fibers from the second, third, and fourth thoracic ganglia, follows the bronchi to their ultimate subdivisions. We have emphasized the fact that in the heart the vagal fibers served to regulate the pace of cardiac contractions, and that, while feeble galvanization or increased adrenal activity, by stimulating the oxidation processes of the vagal bulbar centers, quickened the heart-beats, powerful stimulation arrested them. The same phenomena are obtained under similar conditions in the case of the lungs. As is well known, section of the vagi in the neck causes the respirations to fall to four or five a minute; feeble galvanization accelerates their number, while a sufficiently strong current will arrest the respiratory movements. Barring the special functional attributes of the heart, which in certain particulars influence experimental results, all phenomena strictly ascribable to the vagal supply are repeated in the lungs: a fact which pointedly attests to the similarity of the nervous supplies of the two organs and to a common origin. Still, we must not lose sight of the fact that the peripheral respiratory muscles are the main factors in these phenomena, and that those with which the lungs *per se* are concerned have other objects in view.

In the light of all we have said so far concerning the active functional rôle assumed by the vasomotor terminal branches of general motor nerves, the distribution of vasomotor fibers to the terminal arterioles must play a predominant part in pulmonary functions: one, indeed, of considerable clinical importance. Thus, the plexus which overlies the pulmonary artery and is intermixed with vagal fibers becomes, when considered from our standpoint, the regulative system as regards the amount of *venous* blood allowed to penetrate the lung. As this blood contains the adrenal secretion, this vessel becomes, therefore, one of the most important pathways of the general circulation. This asserts itself when we realize that it is upon the amount of *venous* blood driven into the lungs by the right ventricle, besides the character of this blood, that the efficiency of the respiratory functions depends. Excessive activity of the adrenals increases the power of the heart and vascular tension, the speed of the stream which traverses the lungs is correspondingly augmented, and con-

gestive turgescence of all its vessels must follow. Notwithstanding the fact that not a drop of blood is added to that contained in the system, dyspnœa occurs. Dyspnœa also follows insufficiency of the adrenals,—*i.e.*, of its secretion,—because this involves in direct sequence imperfect oxygenation of the pulmonary blood, inadequate oxidation of the cerebro-spinal centers, relaxation of the vascular channels, etc. Contraction and dilation of the vascular channels being of suprarenal origin, the vasomotor terminals obviously become prominent elements of the mechanism. In fact, it is partly through the intermediary of vasomotor nerves that excessive or inadequate activity of the adrenals is felt in all parts of the organism.

That the suprarenal secretion, through which the right heart is contracted, underlies dyspnœa is well illustrated by the effects of all drugs that are sufficiently active to markedly affect adrenal functions. The action of venoms even more strikingly shows the morbid connection that exists between the impairment of suprarenal activity and pulmonary functions, even the stage of blood-disintegration being sometimes reached. Noé,[27] for instance, refers to the many observers who have reported intense respiratory phenomena after cobra-bites. Viper-venom was also found by Phisalix to produce at first "accelerated respiration," then "somnolence, with slowing of respiration." Bee-venom in sufficient quantity gives rise to dyspnœa, according to Paul Bert, *black blood* being found in the vessels. Toad-, salamander-, scorpion-, and eel- venoms were found to affect respiration in a similar manner. Mosso noted that the process of death varied with the dose: medium doses first arrest respiration, then the heart; stronger doses arrest both simultaneously. Paralysis of the motor end-plates had evidently nothing to do with this process, since Mosso found the thoracic nerves responsive to the induced current.

Removal of the adrenals under these conditions should give rise to phenomena similar to a violent dose of venom. Cybulski not only observed,[28] under these conditions, marked dyspnœa, a fall of the vascular pressure to zero, and hæmo-

[27] Noé: *Loc. cit.*

[28] Cybulski: Gazeta Lekarska, March 23, 1895.

globinuria, but also found that the injection into the veins of an aqueous 10-per-cent. solution of suprarenal extract "immediately caused these phenomena to disappear." Boinet[29] states that after removal of both organs in a large number of rats the respiration became "slow, painful, and difficult." *Black pigment*, ascertained to be similar to that found in the skin in Addison's disease, was found in large quantities in the great majority of the animals examined.

Again, the opposite procedure—*i.e.*, the introduction of suprarenal extract into the circulation—should increase the activity of the cardiac and respiratory functions. Mankowsky[30] noted "a great increase in blood-pressure and stimulation of the cardiac and respiratory centers." This occurred "even when the animals (dogs) were under the influence of chloroform, morphine, or chloral hydrate." "In cats," says Swale Vincent,[31] "by far the most noticeable feature was an enormous rapidity of the respiratory movements in the early stage." The two—now familiar—stages that occur under the influence of toxic doses of suprarenal extract, as well as under that of other poisons, are well illustrated in the following observation by the same investigator: "In the early stage of poisoning respiration is quick and shallow and the heart is excited. Subsequently the breathing and heart-beats become feeble, and finally the respiration is deep and infrequent." Finally, the fact that all these phenomena are independent of the cord has been shown by Biedl,[32] who, as we have seen, obtained marked increase of blood-pressure after injections of suprarenal extract, notwithstanding the fact that all the spinal structures had been removed. These few illustrations, to which many could be added, seem to us to conclusively show that *in general toxæmias dyspnœa is primarily due to impaired activity of the adrenals.*

The evidence available that vasomotor nerves are present in the lungs is exceedingly limited as compared to that recorded in relation to their presence in other organs. And still

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[29] Boinet: *Loc. cit.*
[30] Mankowsky: Russian Archives of Pathol., etc., March, 1898.
[31] Swale Vincent: Jour. of Physiol., Feb. 17, 1898.
[32] Biedl: Wiener klin. Wochenschrift, ix, 1896.

the fact that, as in the latter, vagal and sympathetic fibers are stated by all anatomists to form plexuses as they jointly enter the lungs obviously suggests that these organs are on the same plane in respect to our conceptions as any of the thoracic viscera studied. So generally, in fact, have we found this inosculation to mean combined and correlated function that we have been led to believe that in all organs within the vagal domain general motor functions invariably aim to preserve tonic contraction of arteries and insure adequate nutrition, while vagal functions are as universally intended to incite and govern the *active* stage of these functions.

Clinical evidence tends to sustain this view. It seems to account, for instance, for the following results of section of both vagi in the neck, as outlined by Sappey[33]: "Section of both pneumogastrics in the median portion of the neck not only abolishes the sensibility of the respiratory mucous membrane and paralyzes the internal respiratory muscles; it also involves as consequence a mucous *effusion* into the bronchi, *engorgement* of the lungs, emphysema of these organs, and a very sensible diminution in the number of inspirations." Indeed, the three functions we have ascribed to the vagus, sensory, excitomotor, and vasoconstrictor (while its mate, the general motor, only preserves tonic contraction during *passive* function, and thus insures nutrition), are shown to actually prevail by the results summarized in these few lines. If we now carry this line of inquiry one step further, and recall the sudden overwhelming effusions that sometimes appear in pneumonia, and also—viewing the question from our standpoint—the vasodilating effects of declining oxidation processes of vagal and general motor centers, due, in turn, to rapidly increasing failure of adrenal functions, it will become apparent that both systems must be concerned in vasoconstriction. Again, if the anatomical coalescence of both sets of nerves into plexuses here as elsewhere indicates correlated functions, the fact that the sympathetic fibers do exercise vasomotor influence in the lungs seems suggestive.

The question as to whether vasomotor phenomena actually

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[33] Sappey: "Traité d'Anatomie Descriptive," vol. iii, p. 397.

occur in the lungs remained doubtful notwithstanding the labors of Brown-Séquard, Hofmokl, Lichtheim, and others, until 1881, when François-Franck was able to demonstrate a vaso*constrictor* action of the sympathetic nerves distributed to this organ. Since then Cavazzani, Henriquez, and Rose Bradford and Dean have confirmed the latter investigator's observations. The experiments of François-Franck[34] consisted in stimulating the sympathetic fibers at their entrance into the organ: *i.e.*, the fibers to which we have applied the term "extrinsic." This investigator found that increase of pressure occurred above the area stimulated, while decrease of pressure simultaneously became manifest below the latter. This test, as is well known, is used to determine the existence of vasomotors in other organs. Again, he noted that moderate stimulation of the sympathetic cardio-pulmonary filaments caused lowering of the pressure in the left auricle and increase in the pulmonary artery: a result indicating a vasoconstrictor action upon the intervening vessels.

Further testimony appears when in accord with previously recorded facts we connect the effects observed, not with the sympathetic ganglionic chain *per se*,—the conducting path from the anterior pituitary to the adrenals,—but with the spinal cord. The experiments of Rose Bradford and Dean[35] are thus referred to by François-Franck: "They carefully sought the points of emergence, from the cord, of the filaments which cause elevation of pulmonary pressure and lowering of aortic pressure: that is to say, pulmonary vasoconstriction. These were located from the second to sixth dorsal, and, in respect to maximum effects, on a level with the third, fourth, and fifth nerves. The pulmonary vasoconstrictors ascend the chain up to the first thoracic ganglion, where they become detached, to reach the pulmonary plexuses." A suggestive feature of the topography of these nerves is that the lower limit of the ganglionic chain through which they pass happens to be the upper limit of the ganglia from which the splanchnic

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[34] François-Franck: Lalesque, Thèse de Paris, 1881; and Archives de Physiologie, Oct., 1895.

[35] Rose Bradford and Dean: Journal of Physiology, p. 57, 1894.

nerves that ultimately carry impulses to the adrenals are given off.

We thus have considerable testimony, clinical and experimental, in support of the view that the lungs contain vasomotor nerves. It behooves us now to delineate, if possible, the extent to which each system—general motor and vagal—takes part in the process. The experimental evidence, as we have seen, only refers to the sympathetic fibers as vasomotors, and this coincides with anatomical data. Sappey[36] studied the distribution of vagal nerves in the lungs of mammals, including particularly those of man, the ox, and horse, and reached the following conclusions: "1. They follow the subdivisions of the air-tree to their terminal extremities; they do not leave these subdivisions and follow them to the lobules. 2. All those that leave the anterior pulmonary plexus and the much greater number given off by the posterior pulmonary plexus preserve their plexiform arrangement throughout their entire distribution; their meshes are elongated only in the line of their axis, each thus constituting an elongated ellipse. 3. Their ramifications, essentially destined for the muscular coat of the bronchi and respiratory mucous membrane, have no connection with the blood-vessels." Berdal, on the other hand, confirms this, and indicates the rôle of the sympathetic terminals in the following lines: "The branches of the pneumogastric are destined for the bronchi; the branches of the great sympathetic are lost in the walls of the arteries."

This represents the actual anatomical conditions present, in the light of available evidence, and there is no ground, even from the standpoint of our conceptions, to modify them. It is only when we inquire into the manner in which the two systems of nerves affect function that present teachings and our own views differ. Indeed, we have seen that section of the vagi in the neck caused loss of sensation in the respiratory mucous membrane, paralyzed the bronchial muscles, and gave rise to effusion of mucus into the bronchi and engorgement of the lungs. How can all these phenomena be accounted for without granting sensory, motor, and vasomotor functions to

[36] Sappey: *Loc. cit.*, p. 391.

the vagal supply? Loss of sensation points to inhibited function, and not to engorgement of the bronchial mucous membrane. And yet we may have engorgement without functional erethism, if it is due, not to the presence of blood fully charged with oxygen, but to blood which, through the very fact of being dammed up in the vascular channels, is reduced therein to practically the condition of venous blood. The effusion of mucus into the bronchi and pulmonary engorgement would occur as normal consequences of such a state of things. But how account for this vascular dilation without granting vasomotor attributes to the vagal plexuses? We might incriminate sympathetic filaments were it not in the *neck—i.e.*, above the spinal embranchments—that the vagus was cut. But no error is possible; section of the vagus *alone* gives rise to the phenomena mentioned. It is the terminals of this nerve, therefore, that are alone in question, and the loss of the impulses which they transmit to the subepithelial vessels is accountable for their occurrence.

Again, one of the results of section is "paralysis of the bronchial muscles." Vasomotor nerves, even apart from our own views, are recognized factors of the circulation of any tissue. We have proof of vasodilation in the effusion and pulmonary engorgement as a result of the vagal section. Now, coupling this with the mass of evidence we have submitted that vasoconstriction is the primary factor of functional activity, how can we account for the paralysis of the bronchial muscles without granting the vagus terminals vasoconstrictor functions? Again, the fact that cutting of both nerves in the neck gave rise to paralysis of these muscles points to another suggestive feature, namely: that the vagus must *incite* and *govern* the motor impulses to these muscles, besides presiding over the functional variations of caliber of their vessels. If we now add to these manifestations of *efferent* nervous activity those of *afferent* activity suggested by the loss of sensation over the bronchial mucous membrane, it seems clear that *we have in the vagal nerves referred to an autonomous supply especially devoted to the functions of the bronchial tubes and their ramifications down to*—but not including—*the pulmonary lobule.* The importance of this fact asserts itself when we realize that

it accounts for the complete isolation of bronchial affections from those of the parenchyma, and gives us a clue to their original cause, as we will see later on.

That the structures beyond the domain of the vagus have their own independent mechanism hardly needs to be emphasized by physiological experimentation, so great is the difference between the clinical phenomena witnessed when the lobules themselves are involved in the morbid processes. The old and dreaded "capillary bronchitis" normally assumed a pathological *status* in nomenclature more in keeping with its true identity when it became known as "broncho-pneumonia." Even this term may become obsolete when the link with its next of kin, lobar pneumonia, will be better understood.

Again, a familiar histological fact will serve to show—in the light of our views—how definite is the association between physiological function and disease as manifested in this lobular individual system: The infundibuli, as is well known, are frequently clearly defined by blood-pigment deposits in the connective tissue that separates the lobules. This is because, as we have shown, this is the region where the hæmoglobin constituents find their binding substance: the suprarenal secretion. We have seen the effects of violent toxics—venoms, for instance,—on the blood. The Martinique *fer-de-lance* viper so thoroughly overcomes suprarenal functions as to give the blood the appearance of "prune-juice." What have we in the "rusty," or "prune-juice," expectoration but signs of impaired activity of the adrenals? We shall see that each has its meaning in this particular, and that each represents a stage in the morbid process, but a stage in which the adrenals play the leading part. And so can the hyperleucocytosis, the fibrinous "exudation," the œdema to which we have referred, etc., be traced to the adrenals: overactive at first, then insufficient and perhaps altogether arrested when the general toxæmia—not alone that due to toxins derived from the Friedländer pneumococcus, but to *any* other germ capable of sufficiently undermining suprarenal functions, through its toxins—has reached an advanced stage.

If, therefore, we have isolated the vagal field, it is all the better to emphasize the overwhelming importance of that part

of the pulmonary structures which belongs to the domain of the suprarenal glands—and to the vasoconstrictor nerves that govern the flow of venous blood which carries their secretion to the pulmonary lobules.

If we now retrace our steps, a corresponding identity of the two blood-systems, the *bronchial* and the *respiratory*, will assert itself. The bronchial arteries follow the subdivisions of the bronchi, but only as far as the lobular bronchiole. The terminal arteriole does not penetrate the lobule, but furnishes branches to the pulmonary connective tissue, to the lymphatic ganglia, and to the pleura. This appears to us as an important feature in pathogenesis: The bronchial arteries supply the blood upon which the parenchyma depends for its oxidizing substance. *Insufficiency of the adrenals, therefore, by reducing the oxidation processes correspondingly reduces the nutrition of the pulmonary tissues:* a predominating feature of phthisis.

The pulmonary artery—that containing the adrenal secretion in its venous blood—also closely follows the bronchi and their subdivisions, and only leaves them at the terminal bronchiole, where the alveolar ducts begin and subdivide into the capillary net-works which closely enmesh the alveoli. The net-works thus formed are the closest in the organism. The return *arterialized* blood passes into the venules, which carry it to the pulmonary veins: the channels directly connected with the left auricle.

The veins of the bronchial system, however, do not return their blood, as do similar vessels in other parts of the organism, along the path of their arteries. The capillaries which are distributed to the connective tissue and lymphatic structures between the lobules, etc., return their blood to the superior vena cava by the bronchial veins of the venæ azygos, but those which end at the alveoli anastomose *with capillaries derived from the pulmonary venous tree.* Their blood is thus mixed with that of the lobular capillaries, and is returned to the heart with the—now arterial—blood of the pulmonary vein.

We thus have two distinct vascular systems: the *bronchial*, the arteries of which supply blood to the bronchial and peribronchial structures; and the *respiratory*, the vessels of

which solely subserve the process through which venous blood is converted into arterial blood and are therefore distributed to the lobules.

If we now inquire into the nature of the nervous mechanism through which their functions are governed, we are led —in the light of our own views—to an interpretation similar to that found to satisfy the needs of other organs. The comparison of a pulmonary lobule to a racemose gland is sometimes met with in text-books; examination of a lobule soon shows that its structures sufficiently correspond to that of the glandular organs we have studied to enable us by analogy to ascertain the nature of its relations with nerve-terminals. Miller, we have seen, refers to the "exceedingly fine *capillary net-work* shrunken into the *epithelium* of the air-sacs so that between the epithelium and the capillary there is only the extremely delicate *basement membrane*." Again, he refers to the subdivision of the pulmonary artery "which divides quite abruptly, a branch going to each infundibulum"; from the latter "small *arterioles* arise which supply the alveoli," while these on reaching the air-sac are said to culminate in "the rich system of capillaries to which they give rise." The italicized words but repeat what we have emphasized elsewhere as the integral constituents of all glands. As will be shown later on, however, the alveoli present histological features which further emphasize their identity as parts of an autonomous system.

There is but one feature wanting to complete the mechanism common to glandular structures: *i.e.*, the delicate nerve-terminals distributed to the lobular cells. "The final termination of the nerve-filaments within the pulmonary tissue is still undetermined," says Piersol; but under precisely similar morphological conditions elsewhere in the organism terminal fibrils have been clearly discerned. That the pulmonary lobule should represent an exception to the rule is hardly probable: a view indirectly sustained by the prevailing belief that the mucous surfaces contain "secretory fibers." We have seen that François-Franck, Cavazzani, Henriquez, Rose Bradford, and Dean have ascertained that vasomotor phenomena prevailed in the lungs under stimulation. The implied presence of this class of nerves completes the list of structures that

enter into the functional mechanism of other organs; it seems to us to warrant the deduction that the pulmonary lobules do not differ from the latter either in the manner in which their functional activity is governed or in the processes through which they are supplied with mechanical energy.

But we must lay special stress upon the important functional connection that exists between the pulmonary lobule and the right heart. Indeed, we must not lose sight of the fact that *venous* blood is distributed to the lobules. This venous blood, brought to them by the pulmonary capillaries, only contains adrenal secretion, obviously incapable of insuring functional metabolism of the lobular epithelium. But how, then, is this secured? The answer is not difficult to find after all we have said regarding the processes that obtain in the right myocardium. Indeed, we have in the pulmonary alveolar walls precisely the conditions that prevail in the cardiac wall: *i.e.*, the granules β and the *oxidizing substance* of arterial blood. While the granules β also emanate from the liver, and represent the bulk of those unused in the right heart, the oxidizing substance, instead of being supplied by the coronary, as in the heart, originates from the vessels to which we have already referred: *i.e.*, the *bronchial terminal arterioles*. This anastomosis between the bronchial and pulmonary systems is a generally recognized fact; but its vast importance does not seem to us to have ever been suspected.

May the secretion of the adrenals also produce contractile effects upon the lobular walls? The wealth of elastic fibers in the latter suggests that such might be the case, the purpose being to maintain their tone and insure resiliency after unusual dilation. As we will see in the twelfth chapter, the adrenal secretion is active in various ways in this location.

Collectively considered, however, the various elements of the process may be said to distinctly show that respiration, as regards its chemical phenomena, starts in the adrenals and ends in the pulmonary lobules, with the inferior vena cava, the right heart, and the pulmonary artery as mechanical intermediaries, and thus constitutes an autonomous system.

The following deductions appear to us to embody the principal facts developed in the present chapter as regards the

nervo-vascular mechanism of the lungs and the respiratory process:—

1. The nervo-vascular functional mechanism of the lungs consists of two autonomous, though correlated, systems: the respiratory and bronchial.

2. The respiratory nervo-vascular system is composed of:—

(a) The pulmonary lobules, in the walls of which the blood is oxygenated.

(b) The pulmonary artery and its subdivisions, which bring venous blood, adrenal secretion, and granules β to the capillaries of the lobules.

(c) The pulmonary venules and veins, which return the arterialized blood to the heart.

(d) The general motor nerves and plexuses (sympathetic), which govern the functions of the foregoing structures and the vaso-constriction of all vessels of the pneumo-respiratory system.

3. The bronchial nervo-vascular system is composed of:—

(a) The bronchial arteries, which, by their oxidizing substance, sustain functional energy and metabolism in: (I) the interlobular cellular tissue and its lymphatic vessels and glands, the blood thus used passing to the venæ azygos, by the bronchial veins, thence to the superior vena cava; (II) the bronchi, the terminal ramifications of which only reach to the exterior of the lobules, but anastomose with the pulmonary capillaries of the latter.

(b) Vagal nerves and plexuses, which supply sensation to the bronchial mucous membrane, incite and govern its secretion and the vasoconstriction of all vessels of the bronchial system.

4. The process through which functional energy is supplied to the lobular structures (epithelium, basement membrane, and vascular walls of the lobules) to compensate for the absence of oxygen in the blood brought to them by the pulmonary artery is as follows: The oxidizing substance in the blood of the bronchial terminal branches which anastomose with the lobular capillaries, meets the granules β contained in the blood of the latter; oxidation of the granules ensuing, functional energy is liberated, as it is elsewhere in the organism.

5. The functional oxidation process through which the right heart is supplied with mechanical energy is repeated in the pulmonary lobules, and there is some ground for the belief that the con-

tractile effects of the adrenal secretion on the myocardium are reproduced in the pulmonary lobules, the abundant elastic fibers of the latter acting as contractile elements.

6. The respiratory interchanges that occur in the lobules represent the end-result of a process which includes:—

(a) The production of the adrenal secretion, which provides the blood with its affinity for oxygen.

(b) The admixture of granules β to the venous blood of the inferior vena cava, to insure, with the arterial blood of the coronaries, the oxidation processes through which the right heart acquires its mechanical energy.

(c) The motor functions of the right heart.

(d) The vasomotor functions of the pulmonary artery and its ramifications.

(e) The admixture of the arterial blood of the bronchial terminal artery to the venous blood of the pulmonary capillaries as these reach the lobule.

(f) The oxidation of the granules β in the pulmonary capillaries by the oxidizing substance in the blood derived from the bronchial vessels.

(g) Conversion of the venous blood, as it courses through the lobular capillaries, into arterial blood.

CHAPTER X.

THE POSTERIOR PITUITARY AS THE FUNCTIONAL CENTER OF THE NERVOUS SYSTEM, AND AS THE ANTERIOR PITUITARY'S CO-CENTER IN SUSTAINING THE VITAL PROCESSES.

THE IDENTITY OF THE LOWER BRAIN, OR CENTRAL NERVOUS SYSTEM.

In the ninth chapter we ventured to suggest that none of the medullary nervous centers could be considered as "inhibitory" or "respiratory" in the physiological sense now accorded these terms, and we stated that the phenomena ascribed to these centers were regarded by us as (1) the result of excessive (and therefore pathological) stimulation of the vagus as regards cardiac inhibition, and (2) of the interruption of general motor impulses which the medulla serves to transmit, in respect to the respiratory phenomena. Paradoxical as the statement may seem, our views are confirmed by the investigations of the brothers Weber (1845), who first suggested that the heart could be "inhibited" by stimulation of a corresponding medullary center. Their experiments differed from those we have reviewed in that the cerebro-spinal structures themselves were submitted to the effects of the current, thus concentrating the latter upon the areas in which the "inhibitory" centers were supposed to exist. One pole having been placed in the nasal cavity of a frog and the other on the spinal cord over the fourth or fifth vertebra, the heart's action momentarily ceased, then gradually resumed its normal activity. Approximation of the poles upon the cerebral hemispheres and stimulation of the cord produced no effect upon the heart. "Not until the medulla oblongata between the *corpora quadrigemina and the lower end of the calamus scriptorius* was stimulated," says Professor Porter, "did the arrest take place. Cutting away the spinal cord and the remainder of the brain did not alter the result." Our views are likewise sustained by the effects of experimental injury of the medullary area which Flourens termed *le nœud vital,* or "ganglion of life."

Galen had already noticed that death ensued when a certain spot in the floor of the fourth ventricle close to that which is now known as the center of the vagus was injured. But Legallois and Flourens have added much to our knowledge of its physiological relations, and the spot in question, as we have seen, is still considered as the respiratory center. "The results of various investigations show, however," says Reichert,[1] "that Flourens's area, as well as certain other parts of the medulla oblongata that have been looked upon by others as being respiratory centers, are not such, but are largely or wholly collections of nerve-fibers which arise chiefly in the roots of the *vagal, spinal accessory, glosso-pharyngeal, and trigeminal nerves,* and which, therefore, are probably nerve-paths to and from the respiratory center. Moreover, excitation of the *"nœud vital" does not excite respiratory movements,* but simply increases the tonicity of the diaphragm; nor is the destruction of the area always followed by a cessation of respiration. While the precise location of the center is still in doubt, there is abundant evidence to justify the belief in its existence in the lower portion of the spinal bulb." That we are again dealing with the aggregate of centers to which we have referred as the "vagal system" is clear. Indeed, Flourens located his "vital knot" in an area five millimeters wide *between* the nuclei of the vagus and spinal accessory nerves—again in the *lower end of the calamus scriptorius: i.e.,* a region comprised in the area to which the Weber brothers applied one electrode, the other being in the nose, when cardiac arrest or inhibition was first observed by them.

An interesting relationship seems to us to exist between these two sets of experimental results. Indeed, the area to which we refer as that of the "vagal system" thus becomes the source of antagonistic effects involving the same structures: *i.e.,* the Weber brothers caused arrest of the heart by *overstimulation* (not "inhibition" considered as a physiological function) in the manner defined in the preceding chapter, while the lesion produced by Flourens in the same area, when sufficiently severe, arrested the flow of impulses to and from the heart.

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[1] Reichert: *Loc. cit.,* p. 456.

Flourens's *nœud vital,* therefore, is no more the respiratory center than the area traversed by the current can be called an "inhibitory" area. We are simply dealing with the results of two morbid factors: overstimulation (Weber) and interruption (Flourens) of physiological—and therefore functional —impulses transmitted through the medulla and the cord.

In the fifth chapter reference was made to the fact that the posterior pituitary lobe alone, as shown by Howell, contained an active principle. This lobe, the "infundibular," has long been termed the "neural" portion of the whole organ, and appears to us to anatomically present features that suggest a direct connection between it and the cerebro-spinal centers. Hence the use of the words "physiological impulses transmitted *through* the medulla and the cord." The question becomes all the more worthy of a searching inquiry inasmuch as a casual examination of the mutual relations, anatomical and physiological, of the cerebral structures traversed by the current in the experiment of the Weber brothers suffices to show that the elements thus submitted to excessive stimulation coincide with those which would normally fall under the influence of the posterior pituitary body.

The physiological characteristics of the parts influenced by the current must first be ascertained. In the frog, the distance between the nose and the medulla being very short, a current would implicate all elements in its direct path, considering the character of the structures traversed. In this animal, the lizard, etc., the nasal nervous terminals, the tissues about the floor of the median ventricle and the habendula, appear to us as the paths that would be involved. In man the distance between the olfactory area or the nasal subdivisions of the fifth pair and the medulla is also relatively limited, and the intervening structures are of such a nature as to also allow the current to pass uninterruptedly in a straight path. But the floor of the median or third ventricle, which in its anterior portion overlies the base of the skull and is very thin, becomes what appears to us the inevitable path of free conduction, owing to this proximity of the olfactory bulb and the trigeminal nasal terminals, to the medullary centers. Of special interest to us, however, is the fact that in man (and to a great extent in the

frog) the first structure reached by the current after the nasal structures would be the infundibular portion of the third ventricle: *i.e.*, that connected with the posterior pituitary lobe. Again, and very suggestive, is the fact that these structures and all those falling in the line of the current form part of what Professor Foster terms "in point of origin the oldest part of the brain" and "the central gray matter" which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves." Indeed, we might add that, according to Reichert,[2] "one center has been located in the rabbit in the *tuber cinereum*, which has been named a polypnœic center because, when excited, the respirations are rendered extremely frequent." . . . "Another area has been located in the optic thalamus, in the floor of the third ventricle; this center," says the author, "is believed to be excited by impulses carried by the nerves of sight and hearing, and when irritated causes an acceleration of the respiratory rate."

The more dorsal portion of the current would strike a no less important physiological region. "Next to the central gray matter," says Professor Foster, "and more or less associated with it, comes what is called the tegmental region, of which the reticular formation coming into prominence in the bulb and continued on to the subthalamic region, forms, as it were, the core. Belonging to the tegmental system are numerous masses of gray matter from the conspicuous optic thalamus and the red nucleus in front to the several nuclei of the bulb behind. This complex tegmental system, which may, perhaps, be regarded as a more or less continuous column of gray matter, comparable to the gray matter of the spinal cord, serves as a sort of *backbone to the rest of the central nervous system.*"

The morbid effects of the current become normal consequences when we consider that the structures traversed by it include those that even emotions will disturb. Referring to the posterior portion of the pons, that adjoining the tissues that form the fourth ventricle and which represents the downward continuation of the tegmentum, Professor Duval says: "It is, indeed, to the pons that we seem to be authorized to

[2] Reichert: *Loc. cit.*, p. 457.

attribute the most important rôle in the greater emotional expressions, laughing and weeping, cries of pain: in a word, involuntary manifestations." That the structures such as those penetrated by the current should be suddenly jarred and forcibly thrown into vibratory conditions entirely foreign to their normal vibratory rhythm is manifest. That such jarring, especially when the current follows axially a direction opposite to that of a physiological stream of impulses, should so pervert its normal influence upon the organs to which these impulses are normally distributed—heart, lungs, stomach, etc.—as to temporarily or permanently arrest their functions is not only logical, but in accord with the known effects of electricity upon the more highly developed structures.

And we can also doubtless better understand why respiration still continues very much as usual after removal of the brain above the medulla, and why, indeed, all nervous manifestations other than ideation can persist after such mutilation. While there is no *"nœud vital,"* or ganglion of life, in the sense given these words by Flourens,—*i.e.*, in the spot of the medulla where injury arrests respiration,—and the area so injured is not "the mysterious seat of the unknown principle of life," there is, nevertheless, in this location, not a *locus minus resistentiæ*, but an aggregation of nervous paths from all directions, which an injury can functionally impair or destroy, according to the quantity of tissue involved and the kind of lesion produced. Flourens doubtless caused death; but in looking for death in his experimental animals he doubtless did not treat the *"nœud vital"* with the gentleness of a dove. Death ensued—the result of conditions similar to those produced by the Weber brothers with electricity in the sense that molecular disturbance was produced. Yet the Weber brothers only jarred the naso-bulbar structures, and produced temporary inhibition of cardiac action; being more diffuse, the current spread over greater bulbar surface and did less injury. Flourens's puncture, on the contrary, produced an organic lesion, capable not only of destroying the tissues involved, but also of annulling, by the circumferential compression of the neighboring elements caused, the functions over which the latter preside. Even the process of repair, which at once begins under such

conditions, may lead to a fatal issue, the infiltration throttling, as it were, the paths *to* and *from* organs through which life is sustained. When we consider the small relative size of the fourth ventricle, and the fact that the so-called "vital knot" is located in an area which may be computed only by a few millimeters; when we furthermore recognize that such an injury would thus include the vagal, spinal accessory, glossopharyngeal, and hypoglossal within its radius of morbid influence, death as an injury to the spot becomes a normal consequence. The heart and the entire respiratory system—to refer only to those directly concerned with life's processes—are the mechanisms first functionally arrested.

And yet while obstruction of these few square millimeters of bulbar elements will rapidly destroy life, it is possible, says Professor Foster, in the case of some animals "to remove the cerebral hemispheres and to keep the animal not only alive, but *in good health* for a long time—days, weeks, or even months after the operation!"

There must prevail in this connection, however, another contradictory interpretation of experimental phenomena. Indeed, how can we reconcile the presence of motor *centers* in the cerebral cortex with the ability of an animal from which both hemispheres have been removed to execute the motions ascribed to these areas? That an animal deprived of its hemispheres will do this is graphically shown in the following lines of Professor Foster's: "We may, perhaps, broadly describe the behavior of a frog from which the cerebral hemispheres only have been removed by saying that such an animal, though exhibiting no spontaneous movements, can by the application of appropriate stimuli be induced to perform all, or nearly all, the movements which an entire frog is capable of executing. It can be made to swim, to leap, and to crawl. Left to itself, it assumes what may be called the natural posture of a frog, with the forelimbs erect, and the hind-limbs flexed, so that the line of the body makes an angle with the surface on which it is resting. When placed on its back, it immediately regains its natural posture. When placed on a board, it does not fall from the board when the latter is tilted up so as to displace the animal's center of gravity; it

crawls up the board until it gains a new position in which its center of gravity is restored to its proper place. Its movements are exactly those of an entire frog except that they need an external stimulus to call them forth." It is quite clear that all motor phenomena are carried out, notwithstanding the absence of parts of the brain which have been undeniably shown by experiments in animals, pathological conditions of the human hemispheres, etc., capable of inciting them. The familiar convulsive movements in various parts of the body, trunk, leg, arm, etc., when certain motor areas are stimulated would mean nothing to us if the use of electricity for this purpose were the basis of this doctrine, but *lesions* in these areas have unquestionably proven that they do preside over motor functions, not only in a general way, but in the sense implied by "cerebral localization." How account for the self-evident discrepancy which the entire absence of these structures indicates in present conceptions of the processes involved?

We are brought nearer to a solution when the removal of cerebral tissues—those to which we have referred as jarred by the electric current passed by the Weber brothers between the nose and the bulb—is continued downward until the cord only is left. "Very marked is the contrast," says Professor Foster, "between the behavior of such a frog which, though deprived of its cerebral hemispheres, still retains the other parts of the brain, and that of a frog which possesses a spinal cord only. The latter when placed on its back makes no attempt to regain its normal posture; in fact, it may be said to have completely lost its normal posture, for even when placed on its belly it does not stand with its forefeet erect, as does the other animal, but lies flat on the ground. When thrown into water, instead of swimming it sinks like a lump of lead. . . . When a board on which it is placed is inclined sufficiently to displace its center of gravity it makes no effort to regain its balance, but falls off the board like a lifeless mass." Such a frog moves its limbs irregularly, but one has but to witness such motions to at once conclude that they are aimless, mere random expressions of the inherent power to contract possessed by all muscular tissues, and which even persist some time after death, especially in the case of

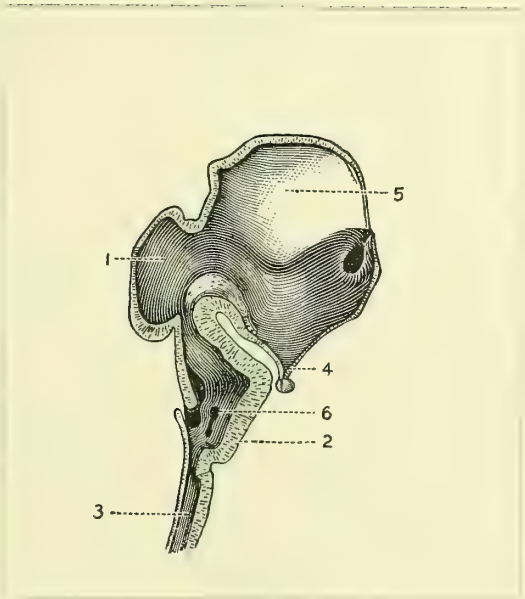
the heart-muscle. Very marked is the contrast, indeed, between this animal and one still endowed with the tissues of the base of the brain. "Pigeons, for instance, have been kept alive for five or six weeks," says the same author, "after complete removal of the cerebral hemisphere with the exception of portions of the crura and corpora striata immediately surrounding the optic thalami." . . . "In warm-blooded animals, as in the more lowly cold-blooded frog, the parts of the brain *below or behind* the cerebral hemispheres constitute a nervous machinery by which *all the bodily movements* are carried out."[3]

That this mechanism is located below the hemispheres in man has also been illustrated by many cases reported, among which may be cited the famous crow-bar case, in which, "by a premature explosion of gunpowder, an iron bar three and a half feet long, one and a quarter inches in diameter, and weighing thirteen and a quarter pounds, was shot completely through a man's head, and perforated his brain. This man walked up a flight of stairs after the accident, and gave his account of how it happened. Although his life was naturally despaired of for some time, he *developed no paralysis;* nor did marked impairment of his intellectual faculties follow convalescence. Eventually he recovered his health. Twelve years elapsed before his death, during which time he was a laborer on a farm."[4] It is thus evident that, *in the entire animal scale, the hemispheres are functionally dependent upon some complemental function located in the base of the brain—in the region through which the Weber brothers passed their heart-inhibiting current: i.e., the central gray matter lining the neural canal.*

A remark which in this connection is of particular interest to us is that of Professor Duval, when, referring to the meaning of bulbar functions, according to modern conceptions, he says: "For the physiologist, the medulla extends above the limits of the vertebral column into the cranium and *about up to* the sella turcica." *We* would say *into* the sella turcica, for it seems clear to us that *the posterior pituitary lobe presents the functional characteristic that would fulfill the requirements of*

[3] The italics are our own.

[4] A. B. Ranney: "Lectures on Nervous Diseases."



MEDIAN AND VERTICAL SECTION OF A THREE MONTHS' EMBRYO. *[Dejerine.]*

1, Aqueduct of Sylvius. 2, Medulla Oblongata. 3, Central Canal. 4, Infundibulum and Pituitary Bodies [the latter have been added to the original]. 5, Optic Thalamus. 6, Fourth Ventricle.

the complemental processes that the functions of the hemispheres demand.

The annexed colored plate, which represents a median and vertical section of the encephalon and bulb of a three months' embryo, distinctly indicates the direct continuation of the cord up to the posterior or infundibular pituitary lobe. The tract connected with the posterior pituitary is colored bluish gray. The pituitary has been added to the infundibular extremity of the original illustration. The relations of the structures which ultimately become the corpora quadrigemina by meeting the posterior part of the third ventricle are well shown.

That our views in this connection are based on a solid foundation is further sustained by the painstaking investigations of Andriezen,[5] who traced a direct connection between the pituitary and the medullary and other more anterior structures through the various phylogenetic stages of vertebrates. The following statements and the table appended are quoted from his paper: "A survey and investigation based on all classes of vertebrates show that the hypophysis occupies the position and relationship to the other structures which may be condensed in the following table:—

"Relation of Pituitary to Other Nerve-centers and Head-structures in Order from Before Back.

Nerve-center.	Olfactory center.	Posterior lobe of pituitary.	The bulbo-spinal centers.
Nerves.	Olfactory nerves.	Hypophyseal nerves.	Bulbo-spinal nerves.
Distribution.	Epithelium of nasal sac.	Pituitary duct gland (anterior lobe).	Buccal, etc., and general subcutaneous.
Body-region.	Pre-oral (prostomial).	Oral.	Post-oral (branchial, etc.) and general body."

[5] Andriezen: British Medical Journal, Jan. 13, 1894.

Of course, this applies to both pituitary bodies, but we have shown that the anterior pituitary as the source of the nervous impulses transmitted through the splanchnics was in reality a nerve-center; and we have further referred to the fact that the pituitary as a whole has long been associated with the nervous system by anatomists, and particularly with the "sympathetic" system by Bourgery and Hirschfeld. That the investigations of Andriezen should have borne but little fruit, so far, is probably accounted for by his statement that "variations in weight bring it under the Darwinian law of panmixia; if so, the indication being, what study of lower vertebrates shows, namely: that it has probably passed the acme of its activity and in man is functioning less vigorously."

We must express our belief, however, that, when man is in question, cessation of natural selection may not always mean that an organ has become useless, but instead that it has reached the acme of perfection. Loss of functional vigor may denote, in this connection, what it denotes in the human hand as compared to that of the gorilla: *i.e.*, gain in functional precision and delicacy.

In the embryo, the posterior pituitary body opens directly *into* the third ventricle through the infundibulum. If during uterine existence "the whole life-achievement of myriads of generations of living things" is represented, the phylogenetic history of this organ should show traces of its ultimate functions. Andriezen found that in the amphioxus its analogue is represented by "a subneural glandular organ, a duct lined by ciliated epithelium which affords a communication between the buccal and neural cavities, and a group of nerve-cells around and at the back of the upper opening where the duct widens into the ventricular cavity." We have here the main primitive structures of the pituitary in man.

Referring to Andriezen's investigations, Berkley[6] says: "He has farther shown that particles of carmine, suspended in the water surrounding the animals, will be taken up with the water *passing through the infundibular duct* and carried by ciliary action *into the ventricle*, and thence into the *central*

[6] Berkley: Brain, Winter, 1894.

canal of the cord; finally the particles of carmine may be traced right up to the free end of the canal, where the spinal cord opens into the exterior by the blastopore; therefore it is made manifest that the infundibular duct carries a stream of oxygen-bearing water for the nutrition of the tissues and the carrying off of their effete products." Alluding to personal studies to which we will presently refer, Berkley then adds: "It is quite curious to find essentially the same structures preserved in as high a vertebrate as the dog, and descending to so low a zoological order as amphioxus, though, as Müller remarks, the pituitary is practically the same *from myxine to man.*" Yet in man the infundibular orifice is *closed*, and the posterior pituitary, during its evolution, must, therefore, have assumed some function other than that possessed by the organ during the earlier phases of its career and of which the earlier forms should also show traces.

We have seen that oxygenation of the blood, the highest development of the function carried out by the water-vascular system in the amphioxus, belongs to the domain of the anterior pituitary. The remaining inference afforded by the phylogenetic history of the organ, therefore, is that *the prospective posterior pituitary body is represented in the amphioxus and amocœtes by the group of nerve-cells around and at the back of the upper opening, where the duct widens into the ventricular cavity.*

We must state that we consider this perfect concordance between the functions of the anterior and posterior pituitaries as we have conceived them and those found throughout the entire evolutional scale of zoological forms as far back as the amphioxus by Andriezen as very strong evidence that our views are sound.

THE HISTOLOGY AND PHYSIOLOGY OF THE POSTERIOR PITUITARY BODY.

What is the physiological relationship between the two lobes? Déjerine[7] states that vertical and horizontal sections of both organs show that they are absolutely distinct and sepa-

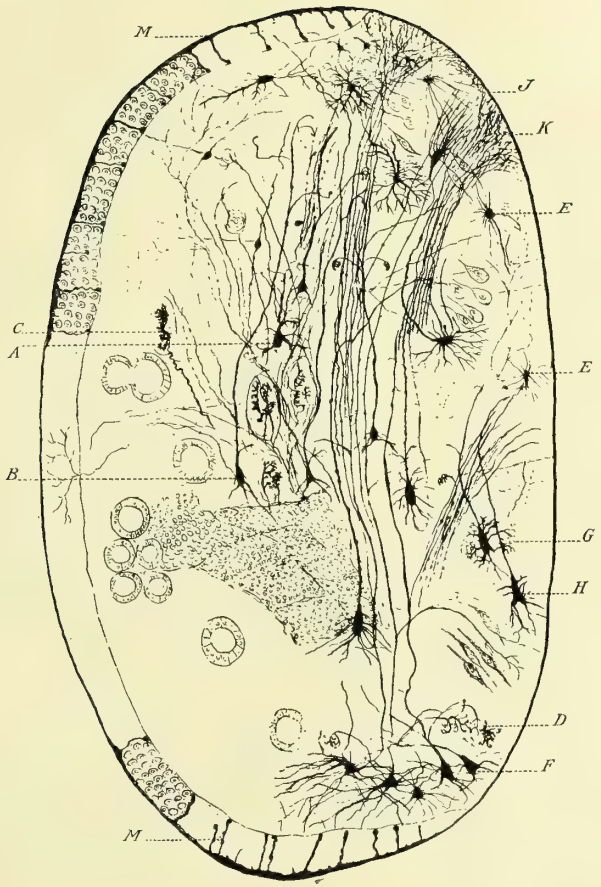
[7] Déjerine: "Anatomie des Centres Nerveux," vol. i, 1895.

rated by a fibrous lamina; and, furthermore, that "the posterior lobe alone is connected with the infundibulum." . . . "It is developed from the brain" and "is a dependence of the middle ventricle." The anterior lobe is only connected with the cerebral structures through vessels which, according to Berkley,[8] "directly pass into it from the *substance* of the infundibulum." The blood-supply of the posterior lobe is also derived from the same source, but it is less rich, though sufficiently so to satisfy the needs of an active function. Indeed, the organs differ mainly in the character and wealth of their nerve-supply—much to the advantage of the posterior lobe, however. The development of the anterior lobe from the ectoderm of the primary oral cavity, instead of, as in the case of the posterior lobe, from the embryonic brain, accounts for what anatomical dissimilarities prevail.

The histological characteristics of the posterior lobe also suggest that it is the seat of some nervous function of a high order. This is well illustrated by the exhaustive study by H. J. Berkley[9] after an examination of some two thousand five hundred slides. A summary of such a work hardly does it justice; we must therefore refer the reader to the original paper for details other than those that we will presently submit.

The outer layer of the organ was found by Luschka and Müller to be composed of gray matter similar to that found over the infundibulum. Berkley refers to this layer as composed of slightly irregular *ependymal* cells three or four deep, through which rather thick ball-tipped filaments penetrate to the second anatomical subdivision of the lobe. This outer coating of cells does not extend around the entire lobe, however, but covers only its free, or posterior, surface. Its anterior portion, that nearest the partition between the two lobes, has no such covering, so that its elements appear to be in contact with the partition itself or to be only separated from it by its capsule. The second subdivision of the posterior organ occupies, judging from Berkley's drawings, about one-third of its mass, and recalls, as to structure, that of the anterior lobe.

[8] Berkley: Brain, Winter, 1894.
[9] *Ibid.*



VERTICAL SECTION OF THE POSTERIOR PITUITARY BODY. *[Berkley.]*

Somewhat diagrammatic to indicate various types of cells.
Its normal size is that of a small pea.

[*Brain.*]

Again do we find the closed glands, or alveoli, including the colloid substance. Again are the glandular elements supported by connective-tissue trabeculæ permeated with capillaries, though the caliber of the larger vessels is somewhat smaller. Yet—a feature which seems to us important—the colloid alveoli are always most numerous near the outer edge of the ependymal cells, that portion farthest away from the interlobular partition, while the space between these structures and the partition is occupied by cellular elements of an entirely different kind.

The third portion may be said to occupy nearly two-thirds of the entire lobe: a perfect maze of nervous elements, some of which have not so far been found elsewhere in the organism. Yet connective-tissue partitions carrying blood-vessels are discernible throughout this entire area: a feature which suggests that an orderly subdivision exists. Its nervous elements vary greatly in form, but they may be divided into three general classes: 1. Cells that give off protoplasmic extensions, neuraxons, etc., that are not sufficiently long to reach the upper, anterior region of the lobe: *i.e.*, the infundibular region. 2. Cells the extensions of which reach this region. 3. Cells that are found mainly or only in this portion of the organ.

The *first class* includes flask-like cells with knot-tipped fibers that recall those of the anterior lobe (Fig. *A*, Plate I, and Fig. *a*, Plate II). These bodies are widely distributed, but their multitude of ramifications end freely among neighboring structures. Similar, though smaller, cells (Fig. *B*, Plate I, and Fig. *b*, Plate II) are found chiefly in the center, and have processes that extend upward a considerable distance and there often terminate in a brush-like figure. In this class may be included peculiar oval bodies (Fig. *C*, Plate I, and Fig. *c*, Plate II), mainly found in the center of the organ, that recall closed follicles. They give off axis-cylinders that coil about them irregularly, and fibers which terminate either in irregular figures resembling combs with knob-tipped teeth or in cat-o'-nine-tail-like tufts. Neuroglia cells, especially those of the mossy kind, are shown in Fig. *d*, Plate II, while spider-cells (Fig. *E*, Plate I, and Fig. *e*, Plate II) are mainly found where the nerve-cells are very numerous: *i.e.*, the anterior third

of the lobe. The spider-cells, however, which only differ from those found in the cerebral tissues by their larger size in proportion to the length of their tentacles, outnumber the other cells as the upper infundibular region of the lobe is reached.

The cells included in the *second class* are all, as stated, distinguished by one or more protoplasmic extensions, which insinuate themselves between all the elements intervening between their starting-point and the infundibular area referred to, where they break up into figures. The lowermost of these, the ganglion-cells shown in Fig. *F*, Plate I, and Fig. *f*, Plate II, exemplify this type very well, since their extensions traverse the entire organ in an upward direction and end in the upper infundibular area. Higher up in the organ large pyramidal and oval cells are found (Fig. *G*, Plate I; Fig. *g*, Plate II; and *g*, Plate III), the terminal subdivisions of which break up into exceedingly fine feathery filaments. The only axis-cylinder of this cell, after distributing a few branches to neighboring elements, continues upward and subdivides, when near the upper margin of the infundibular region, into a complex net-work which entwines the alveoli found there. A third type, characterized by short dendrites and many hair-like processes (Fig. *H*, Plate I, and Fig. *h*, Plate III), is found throughout the entire nervous area and also gives off one long dendrite, which extends a long distance upward and forward; this extension may possibly reach the infundibular region or its neighborhood. Coming from every direction, these long dendrites seem, at any rate, to point all toward this one region. The other dendrites are short and distinguished by the presence of more or less numerous hairy processes, while some of the terminal ramifications are ball-tipped—suggesting a possible identity as collectors of energy, which, transformed in the body of the cell, is directed upward by the long dendrites.

In the infundibular region of the lobe—*i.e.*, the cellular elements of the *third class*—the final ramifications of the long dendrites form an extremely complex aggregation of tufted figures, wavy threads, and feathery protoplasmic ramifications. In the midst of this maze of nervous elements certain cells are to be found, the like of which Berkley has not been able to detect in any part of the central or peripheral nervous system.

VARIOUS TYPES OF CELLS IN THE POSTERIOR PITUITARY BODY. *[Berkley.]*

[*Brain.*]

They are small and round, and give off strong dendrites, which appear knotted or covered with thorns, giving them a "prickly appearance" (Fig. *J*, Plate I, and Fig. *j*, Plate III). Another variety found in abundance in this region is a small cell with a rich, apical tuft of fine, wavy processes. They are also distributed in the midst of a net-work of varicose nerve-fibers (Fig. *K*, Plate I, and Fig. *k*, Plate III) in the upper and near the anterior border of the lobe "along the space formerly occupied by the infundibular duct." As already stated, the spider-cell is to be found in great abundance in this locality, which, added to the other two varieties of cell, gives us three main cellular elements as representatives of the class of cells found mainly or only in the upper infundibular region of the organ.

What is the nature of the organ's functions? That it is not a secreting organ seems obvious; there is no evidence that it contains ducts. May it produce an internal secretion? The vascular channels, intrinsic and extrinsic, are smaller than those of the anterior lobe, and the latter does not produce an internal secretion. Such being the case,—notwithstanding its far greater vascular supply and a much less complex nervous organization,—it is not likely that its mate, the posterior lobe, should be the seat of such a secretory function. Indeed, the embryological development of the latter and its anatomical relations disprove this completely, while they pointedly suggest a marked kinship with the anterior lobe as to intrinsic function: *i.e., as a center for the conversion of chemical energy into mechanical energy*,—a perfectly logical deduction when we note the presence of the same closed glands, or alveoli, including the colloid substance, and their close anatomical relationship. Indeed, everything tends to suggest that, what the anterior pituitary body is to the adrenals, the posterior pituitary body is to the general nervous system.

And, yet, what is the connecting structure between the posterior pituitary body and the parts to which, under such conditions, its energy would be supplied? There is no evidence, according to Berkley, that any of the nervous elements of the infundibular lobe itself pass beyond its limits into the infundibulum. His histological work shows that, while "all the axis-cylinder processes and the long dendrites have a gen-

eral tendency upward and forward, both dendrites and neuraxons branching as they proceed onward, all traces of the dendrites of the inferior and median cells of the lobe are lost some little distance below the superior edge." After an allusion to the vessels and fibrillated tissues that connect the infundibulum with the posterior lobe, he says, "the whole arrangement of the structures of the infundibulum" is "here altered"; then, referring to both lobes,—*i.e.*, the hypophysis,—remarks, "elsewhere it shows no break in the described arrangement, the line of differentiation between hypophysis and infundibulum being sharply drawn, a layer of coarse connective-tissue bundles being placed between and separating the glandular and other structures of the pituitary from the tissues of the infundibulum." It is clear that discontinuity of tissue is a necessity in this location: a suggestive point in itself, since Nature does not take such pains to isolate adjoining structures without an object.

Notwithstanding this striking autonomy of the organ, there are several features in its histological make-up that may enable us to detect the connecting-link between it and the infundibular structures. Berkley refers to the "outer lamina of slightly irregular ependymal cells (Fig. *M*, Plate I) three or four deep, arranged after the manner of the *cuticular epithelium*."[10] This lamina, which older anatomists considered as a continuation of the ventricular gray substance, only covers, we have seen, the free portion of the posterior lobe and is not continuous with the infundibular ependyma. Again, "there are seen, extending from the thin capsule surrounding it" (here Berkley alludes to the *capsule* that surrounds the entire posterior lobe), "numbers of rather thick varicose threads, all unbranched, and invariably ending, when their terminations can be discovered, in a ball-shaped figure, at a definite line in the substance of the body, usually at the *inward* ending of the first layer of epithelial cells, at the line of separation from the more centrally situated elements. These knobby threads," he says, "strongly resemble the ependymal glia-cells of embryonic life, and possibly may be related to them; but, as their

[10] All italics are our own.

VARIOUS TYPES OF CELLS IN THE ANTERIOR AND POSTERIOR PITUITARY BODIES. (Berkley.)

Figs. h, j, k, and g: Cells in the Posterior Pituitary Body. Fig. l: Portion of Glandular Elements of the Anterior Pituitary Body.

[*Brain.*]

basal end is shrouded in a blackened aggregation of cellular masses, their histological origin must remain a matter of some uncertainty."

If, with these histological data before us, we examine Plate I, a suggestive fact asserts itself: *i.e.*, that the lamina of ependymal cells referred to forms a skull-cap-like covering for the second, or secretory, portion of the posterior lobe. The glandular alveoli of the latter, with their colloid substance, are, therefore, in the best possible position for the reception of any nervous impulse that the ependymal cells may be able to transmit outwardly. This is emphasized in Plate I, which shows that this layer exactly covers the entire surface of the secretory region without reaching beyond its limits. The secretory region of the posterior lobe thus seems to be held in the grasp, as it were, of its ependymal covering, which in turn contains the nervous, "rather thick, varicose threads." This suggests that the capsule may not be the insignificant structure it is now thought to be. Even the fragmentary data we have concerning it tend to indicate that it plays an important rôle in the functions of the organ.

Mere protective structures are usually detached without much difficulty from the underlying tissues; Berkley states, referring to the posterior body: "This lobe is so strongly adherent to the dura that it pulls out of the rest of the pituitary body in removing this with the brain, unless the membrane is dissected with it from the base of the skull." Since the capsule is the part of the lobe so strongly connected with the dura, it must as firmly adhere to the layer of ependymal cells beneath; otherwise efforts at removal would tear it away from the latter. This firm hold of the capsule on the cellular layer is fully accounted for by the thin, fibrous partitions the former sends through the latter, but this in itself suggests an intimate relationship between capsule and cellular layer, especially since the "blackened aggregation of cellular masses," referred to by Berkley, which form the basal extremities of the nervous "threads," all terminate in what appears to be, in his drawings, thickenings in the capsule proper. That such a relationship between the capsule and the nervous elements must exist is further shown by his reference, in the descriptive text of the

illustration, to the "capsule of the lobe thickened in places, *from which* extend threads that end in knobs," etc. That the varicose threads and the capsule are structurally continuous, the latter thus dipping, through a multitude of protoplasmic projections, into the deeper elements of the lobe is evident.

We have, we think, firmly established the relationship between the *anterior* pituitary and the adrenals, through nerves at present considered as appurtenances of the sympathetic system. That the anterior lobe contains but one kind of nerve connected with this function—besides its vasoconstrictors—is shown by the following statement of Berkley's: "In the glandular portion of the body, nerves, other than those belonging to the sympathetic system, are not found. They are very fine *varicose* fibers, with numerous ramifications and branchlets coming off from the main stems at a right or slightly obtuse angle." These fibers must, therefore, represent, considering their relation with the suprarenal system, not terminals of the connecting nerves and distributors of energy, but *collectors* of energy, which the organ's cells have converted into mechanical energy: *i.e.*, impulses for the adrenals. If Fig. *l* in Plate III, which represents a section of the glandular portion of the anterior lobe, is consulted, it will be seen that these nerves present the two main characteristics of the capsular threads of the posterior lobe: *i.e.*, they are also varicose and their tips are likewise knobbed. Since, therefore, the nerves so disposed in the anterior pituitary are collectors of energy, *the varicose and knobbed threads of the capsules of the posterior pituitary must also be collectors of energy.* This is further sustained by the analogy between the two organs to which reference has already been made.

That a direct nervous connection between the posterior pituitary and the infundibular tissues, etc., exists by way of the capsule of the former is apparent. This makes it possible for impulses generated in the depths of the lobe to reach the ventricular structures, irrespective of the sharply defined connective-tissue separation between the lobe proper and the infundibulum. Indeed, such a separation seems a necessity, inasmuch as an impulse, transmitted through the intermediary of the capsule must, owing to the skull-cap shape of the latter,

come from every part of the underlying structures and only reach the cerebral elements through paths that are continuous with the capsule's tissues. Again, the organ's vessels penetrate it by way of the infundibulum; the vasomotor supply of these vessels requires protection from the powerful stream of impulses to which the organ's intrinsic structures give rise. That a profuse padding of cellular tissue is Nature's resource under such conditions is well illustrated by the following remark of Déjerine's: "The vessels of the central nervous system are surrounded by two sheaths of a different kind: the *internal* is connective in nature and belongs to the mesodermic layer; the *external,* neurogliar in nature, is developed at the expense of the external, or ectodermic, layer."

Berkley, referring to the various cellular structures in the deeper portion of the lobe supplied with long extensions, says: "The axis-cylinder extensions of all the cells in the inferior portion of the lobe turn upward. . . . Those belonging to the larger proportion of the smaller cells of the superior border turn upward and intermingle with the marginal fiber net-work. . . . All the axis-cylinder processes and the long dendrites have a general tendency upward and forward, both dendrites and neuraxons branching as they proceed onward: but all traces of the dendrites of the inferior and median cells of the lobe are lost some little distance below the superior edge, and then the neurons only are intermingled with the extensions of the smaller superficial cells, passing them, however, before the border is finally reached, where they spread out into a most extensive fret-work of fine *varicose* fibers, still retaining something of their previous longitudinal arrangement from the threads of the uptending fibers being coarser than the lateral and intermingling branches. It is doubtful whether any of these fibers pass beyond the limit of the lobe into the infundibulum; our sections give no evidence of such an arrangement." This upward tendency of all cells, and the evident concentration of their functional activity at the upper extremity, seem to us to further emphasize the identity of the posterior lobe as a powerful source of energy. Its junction with the end of the infundibulum becomes, under these circumstances, the normal pathway for all the energy that the

organ can accumulate. Capsule and protoplasmic extensions or processes all serve a similar purpose, but the neck of the organ is its own functional limit.

We must not lose sight of the fact, however, that other nerves penetrate the organ. Berkley says, in this connection: "while, on the other hand, the nerve-fibers accompanying the larger arteries are sometimes distinctly seen coming from the infundibular tract into the body of the posterior lobe of the gland and ramifying through it." That there is no connection between these and the nervous structures previously described, however, is shown by the additional statement: "Connections between the fibers of the vascular supply and the nerve-cells of the organ we have never been able to observe. That these are the nerves through which the organ receives its own functional energy—*i.e.*, the impulses to its vessels and alveoli,—as in the case of other organs, is probable."

The prevailing view that the embryonal supporting substance of the brain and spinal cord, the ependymal neuroglia, almost entirely atrophies and disappears in the adult mammal would tend to counteract our belief that the capsule and its underlying structures are important factors of the posterior lobe's functions. Berkley, alluding to the writings of various observers in this connection, and referring to the infundibulum and other tissues of the third ventricle which he had just described, says: "After reading these statements, it was something of a surprise to find the above-described beautiful specimens of several types of ependymal neuroglia extending from *all portions of the middle and inferior regions of the cavity of the third ventricle* and reaching to the periphery, all portions, bodies, branches, tentacles, and subpial endings being readily distinguishable. The region examined is, therefore, very interesting not only from the great variety of neuroglia-cells that may be seen within a very limited area, but from the fact that varieties of the ependymal neuroglia-cells, *previously supposed to have entirely disappeared* from the central nervous system *in the adult* mammal, are found present in perfect condition in the brain of a very high order of animal, and *are not confined, as has previously been supposed, to those of adult reptiles, amphibia, and fishes.*"

If all the data we have submitted are considered collectively, it seems to us that the following conclusion is warranted: *Removal of the hemispheres in an animal does not arrest its power to execute normal bodily movements under external stimulation, because these movements are dependent upon functional structures situated in the lower part of the brain and in the spinal cord and which the posterior pituitary body governs.*

Of course, this appears to contradict at once a great mass of experimental and clinical testimony, but the contradiction is only apparent. Removal of the motor region in the rabbit gives rise to no detectable differences in the movements; the injured animal is similar to an intact one. In the dog, the same procedure, says Professor Foster, causes "loss or diminution of *voluntary* movement in the corresponding part of the body"; but this is only temporary, and the animal may recover to such a degree that the temporarily paralyzed limb cannot be told from the normal one. Careful examination of the brain after death shows that no regeneration of the lost part had occurred. Even removal of the whole motor area causes no appreciable difference between the movements of the two sides of the body to a casual observer. In the monkey the results have been unequal: "While in some instances recovery of the movement has, in the monkey, as in the dog, after awhile taken place, in other instances the 'paralysis' has appeared to be permanent." . . . "The facts, however, within our knowledge relating to the permanence of the effect are neither numerous nor exact enough to justify at present a definite conclusion," says Professor Foster. "On the other hand, the positive cases, where recovery has taken place, are of more value than the negative ones, since in the latter the recovery may have been hindered by concomitant events of a nature which we may call accidental." We might add that a single case of recovery in the monkey, when the motor area has been completely removed, demonstrates that, generally speaking, the structures are functionally similar in all higher animals, including man, judging from such instances as the crow-bar case, or one reported by Brown-Séquard,[11] in which an entire

[11] Brown-Séquard: Société de Biologie, 1876.

lobe was destroyed and in which the only symptoms were amaurosis and slight headache. This emphasizes the identity of the cerebral hemispheres as an aggregate of centers which record impressions and are the seat of reason, intelligence, and volition, but it also suggests that the word "motor" is only applicable in its literal sense to the areas in the lower cerebral mechanism: *i.e.*, the intermediary through which the mandates from the hemispheres are executed.

We have previously referred to the misleading information afforded by the use of electrical stimulation. Nowhere in the organism does this seem to be more applicable than to the brain. This feature and the complexity of the processes involved are fully emphasized in the following lines of Professor Foster: "Some writers appear to entertain the conception that in a voluntary movement, such as that of the forelimb, all that takes place is that the 'will' stimulates certain cells in the cortical area, causing the discharge of motor impulses along the pyramidal fibers connected with those cells, and that these motor impulses travel straight down the pyramidal tract to the motor fibers of the appropriate nerves, undergoing possibly some change at the place in the cord where the pyramidal fiber makes junction with the fiber of the anterior root, but deriving their chief, if not their whole, co-ordination from the cortex itself: that is to say, being co-ordinated at their starting-point. That such a view is untenable and that the simplicity of the electrical phenomena is misleading are shown by the following two considerations, among others: On the one hand, as was shown in a previous section, the co-ordination of movements may be carried out apart from the cortex, namely: in the absence of the hemispheres; and we can hardly suppose that there should be two quite distinct systems of co-ordination to carry out the same movement: one employed when volition was the moving cause, and the other when something else led to the movement. On the other hand, the analogy of speech justifies us in concluding that the cortical processes do take advantage of co-ordination effected by the action of other parts of the nervous system."

Referring directly to the general character of the processes involved, Professor Foster says: "Hence, while admitting, as

we must do, that in the intact animal the cortical area and pyramidal tract play their part in carrying out voluntary movements, their action is not of that simple character supposed by the view referred to above. On the contrary, we are driven to regard them rather as links—important links, it is true, but still links—in a complex chain. As we have already urged, we may probably speak of the changes taking place in the pyramidal fibers as being, on the whole, of the nature of efferent impulses; but *we would go beyond the evidence if we concluded that they were identical with the ordinary efferent impulses of motor nerves.*"[12] All the features emphasized in these quotations, especially in the last lines, appear to us to isolate the hemispheres from the *source* of motor impulses *per se*, and to confirm what experimental evidence obtained after removal of the hemispheres had suggested: *i.e.*, that the *lower* cerebro-spinal structures constitute the executive intermediary through which the cortical mandates are actively realized. Yet, as is well known, these lower structures, in turn, manifest their activity through the centers imbedded in them; what is there to replace the energy in the form of motor impulses which is erroneously supposed to be awakened by the "will" in "certain cells of the cortical area"?

Professor Foster partially answers this question when he says: "The discussion in a previous section has shown that much of the co-ordination of the body is carried out by the middle portions of the brain, and on these the motor area must have its hold as on the spinal mechanisms. The details of the nature of that hold are at present unknown to us." It would appear from the facts reviewed that what might be termed the *central* brain and the spinal cord constitute an entity—a mechanical entity, perhaps—made up of working centers, beginning with the olfactory bulb and the other nervous structures distributed to the nasal mucous membrane anteriorly, and terminating with the end of the spinal cord: *i.e.*, the neural tract of lower forms. Motility, unconscious co-ordination, and sensation—but only, in the case of the latter, to the extent of *transmitting* sensory impressions to their re-

[12] The italics are our own.

spective perception-centers—would enter within the scope of this central brain.

As to the source of the transmitted energy or impulses,—apart from the sensory connections with underlying structures which the cortex possesses,—the predilection of most writers to ascribe to the cortical areas motor functions but demonstrates the need of such an agency to logically account for the phenomena witnessed. To ascribe to the central brain or its centers *per se* attributes of a similar kind would simply amount to shifting to it a convenient, but unknown, quantity, and a fictitious one besides, in the sense that it supplies nothing to account for something. In the only nervous system that we have so far traced to its origin, that of the suprarenal glands, the conversion of chemical energy into nervous impulses was found to be a functional attribute of the anterior pituitary body. That so extensive a system as that represented by the central brain and cord should likewise need a center such as that represented by the posterior pituitary body for the conversion of some form of energy of external source to satisfy the needs not only of its efferent, but also its afferent, impulses seems clear.

That the middle brain is the source of the motor phenomena witnessed is not only suggested by the fact that normal muscular contractility promptly recurs after removal of the hemispheres, but also by the following experiment by Professor M. Duval: "If a part of the gray substance of the cortex designated as the center of certain movements is cauterized, the same movements are obtained when the electrodes are applied upon the eschar thus produced. . . . This experiment shows," says the author, "that the gray cortical substance is not a necessary experimental condition for the production of localized movements." Indeed, he states that the underlying white substance of certain parts will also cause circumscribed motions in certain groups of muscles, etc.

Can the removal of the cortex of one side be followed by the assumption of compensative functions by the opposite side? After the usual period of paralysis, due to shock, the normal motions promptly recurred, precisely as they had on the other side. To ascertain whether the cortex at all possessed motor

attributes Vulpian passed an electrode through it, that part in contact with the cortex being insulated. The underlying white substance was thus alone stimulated. He found that the latter was far more easily excited than the cortex. It seems clear that in these experiments *the increased excitability was due to the closer proximity of the central brain.* "All the functions of the brain can persist," says Brown-Séquard, "after the complete destruction of an entire lobe."[13] Experimental and clinical evidence, however, only eliminate motility and co-ordination from the hemispheres. The cortex, as regards cerebral localization, merely loses the "motor" attribute suggested by the term "motor area," and is shown, by its functional relations with the underlying structures, to be a vast sensitive surface, to the "areas" of which the term "sensory" might be more fittingly applied.

The practical bearing of this may be illustrated by an experiment that will recall some of the familiar features of the earlier portions of this work and at the same time point to the central brain as the source of motor phenomena. This experiment, referred to by Professor Foster, is as follows: "It has been observed that in certain stages of the influence of morphine the cortex and the rest of the nervous system are in such a condition that the application of even a momentary stimulus to an area leads not to a simple movement, but to a long-continued tonic contraction of the appropriate muscles." This, we now know, is due to suprarenal overactivity induced by the drug. Cerebral hyperæmia, we have seen, is the source of the majority of phenomena that follow the ingestion of drugs that are sufficiently active to stimulate the adrenals. The intense headache of quinine and other agents is obviously due to this congestion of the cerebral vessels; muscular contractions, tetany, etc., are also familiar results of suprarenal overactivity; indeed, digitalis, one of the most active suprarenal stimulants, is particularly active in predisposing muscles to contraction and in experimental animals suitably dosed a minimal current without the drug will produce maximum effects

[13] M. Duval: *Loc. cit.*, p. 115.

—prolonged tetany—with it. Strychnine is even more powerful in this particular, as is well known.

In the course of the statements to which we have referred, Foster, after ascribing the temporary paralysis observed after operative interference to a condition "of the nature of shock," remarks: "But, even giving full weight to this consideration, there remains the fact that the cortical area is *associated* with various co-ordinating and other nervous mechanisms belonging to the limbs by such close ties that these are thrown into disorder when it is injured. And, side by side with this, we may put the remarkable fact, previously stated, that during an *abnormal* condition of the cortical area—stimulation of the area—instead of producing the appropriate movements confined to the limb may give rise to movements of other parts *culminating in epileptiform convulsions.*"[14]

If the word "associated" is given its full meaning, limbs and co-ordinating mechanism constituting one class, and the cortical surface the other, *the hemispherical mantle of gray matter being considered solely as a great sensory surface,* the demands of experimental evidence seem to us to be satisfied. What are epileptic convulsions after all but manifestations of excessive *motor* activity? . . . Can the latter be credited to the cerebral cortex, as is now taught in text-books? Obviously not, since experimental evidence proves that the cortex has no motor properties *per se.* But irritation of this sensory surface or an accumulation of physiological toxics, which periodically becomes sufficiently great to so stimulate the suprarenal system as to cause violent hyperæmia, not only of the sensory cortex, but also of its executive mechanism, the middle brain, are the clearly defined causes to which physiological and chemical evidence points. Could the cortex without the middle brain give rise to the same phenomena? That such is not the case is shown by the preservation of all motor functions, including co-ordination, after removal of the hemispheres. Indeed, it is only when the middle brain is removed that the experimental animal thus deprived of its sentient cortex and of its dynamic center practically loses its identity as a living thing. Hence it seems clear that *the motor phenomena caused*

[14] All italics are our own.

by stimulation of the motor areas of the cortex are manifestations of activity of the lower or central brain, incited therein by sensory impulses from these cortical areas.

What constitutes this middle brain? The co-ordination, so evidently preserved in animals deprived of their hemispheres, points to the cerebellum as a possible member of the group of organs to be considered in this connection. Including this organ, therefore, and beginning with the anterior structures, we would now have: the posterior pituitary body; the infundibulum; the central gray matter, forming "a bed for the development of the nuclei of the cranial nerves"; the tegmental system,—*i.e.*, the reticular formation in the medulla continued to the subthalamic region, and to which belong the red nucleus and other bulbar nuclei. All this forms what Professor Foster characterizes as "a more or less continuous column of gray matter" connected with the spinal cord by various ties, besides being, as it were, "a continuation of the spinal gray matter." It is as evident that the optic thalami and corpora quadrigemina are also members of the group, since these related organs appear to be necessary for the success of the experiment in which both cerebral hemispheres are removed. Thus, referring to the frog, Foster says: "In this animal it is comparatively easy to remove the cerebral hemispheres, including the parts corresponding to the corpora striata, leaving behind, intact and uninjured, the *optic thalami* with the optic lobes, the representatives of the *corpora quadrigemina*, the small cerebellum, and the bulb. If the animal be carefully fed and attended to, it may be kept alive for a very long time: for more than a year, for instance."

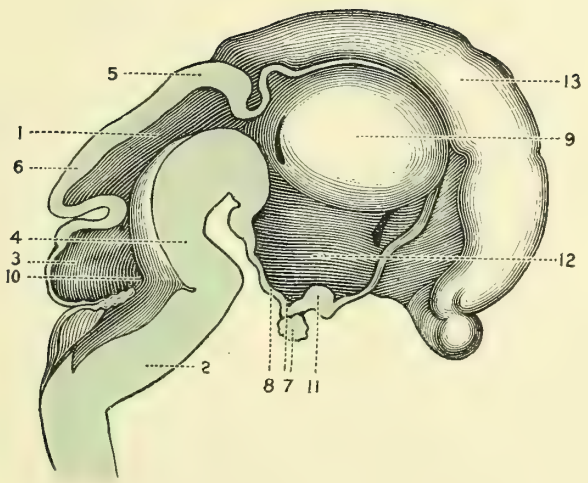
If, with this list before us, we now examine the annexed illustration, originally from His's work, and, therefore, not recently drawn, a rather suggestive coincidence appears, indicating, perhaps, a total independence, in the embryo, of the region containing all the structures enumerated from the vesicle which subsequently develops into the hemisphere of the same side. In mammals the latter is at first insignificant, but it develops very rapidly, soon overlapping the middle structures. The outline of the latter is colored bluish gray. The name of each part is given on the cut: a feature that will

better convey the mutual relations of the various structures included in this system than a verbal description.

Again, the location of the posterior pituitary at the very head of the entire spinal system, as shown in the illustration, adds further testimony to that already submitted to demonstrate the functional relationship between the nervous structures lying in the posterior pituitary, including the floor of the fourth ventricle, and the bulb.

To ascertain this was the main purpose of our inquiry into the comparative functional attributes of the hemispheres and the middle brain. But we must not lose sight of the fact that, in doing this, we have also given *nerve-impulses* their true identity as *mechanical energy: i.e.*, energy similar to that supplied to the suprarenal system by its center, the anterior pituitary. That a center for the conversion of chemical energy into mechanical energy should be necessary for a relatively short nerve-path as is that of the suprarenal system indicates the physiological need of such a center as a source of energy for all nerves.

A summary of all these facts, *i.e.*, (1) that the posterior pituitary body has a phylogenetic history which distinctly identifies it as a part of the entire neural tract; (2) that it presents clearly defined histological characteristics of an active neural organ; (3) that these characteristics extend to the infundibulum, the tuber cinereum, the floor and sides of the third ventricle; (4) that these structures are continuous with the reticular substance of the tegmental region, the medulla, and the cord; (5) that the posterior pituitary body has been found to be in direct relation with the olfactory center and the bulbo-spinal axis in all classes of vertebrates; (6) that a current passed between the olfactory and bulbar centers may cause heart-inhibition and death; (7) that all the nerve-centers are included in the structures with which the pituitary is functionally connected in all vertebrates; and finally (8) that death is caused by a puncture in the region of the vagal bulbar center through interruption of the efferent and afferent impulses through which the cardio-pulmonary system is incited to activity and governed, seems to us to warrant the conclusion that:—



MEDIAN AND VERTICAL SECTION OF A TWO AND ONE-HALF MONTHS' EMBRYO. *[His.]*

[Considerably Enlarged.]

1, Aqueduct of Sylvius. 2, Medulla Oblongata. 3, Cerebellum. 4, Pons Varolii. 5, Anterior Tubercula Quadrigemina. 6, Posterior Tubercula Quadrigemina. 7, Infundibulum and Pituitary Bodies. 8, Tuber Cinereum. 9, Optic Thalamus. 10, Fourth Ventricle. 11, Hypoglossal Nerve [Twelfth Pair]. 12, Third Ventricle. 13, Hemisphere Vesicle.

The posterior pituitary body is the general center of the organism from which all the nervous energy transmitted by the bulbar centers arises.

All the above evidence and the various facts that we have not included in the summary which sustain the conclusion just submitted being of a physiological kind, it seems evident that we should, in view of the important functions ascribed to the organ, also be able to adduce clinical evidence. It is perhaps needless to say that the testimony available can only be indirect, the prevailing belief that the organ is not endowed with physiological functions having kept it out, as it were, of the clinical field. And yet if it holds the important relation to the nervous system we believe it does, its influence in the pathogenesis of general neuroses must be very great. No disease having so far been associated with this lobe, our only hope lies in our being able to discern among the symptoms of typical disease of the anterior lobe what signs might be assigned to implication of the posterior, with which it is intimately blended.

It is interesting to note, in this connection, that quite a number of exceptionally able clinicians—von Recklinghausen, for instance—have considered acromegaly as a trophic neurosis, the organic disease of the pituitary being considered by them as secondary. Again, the neural canal of lower forms led Collina[15] to suggest that the hypophysis (as a whole) also produced a fluid capable of nourishing nervous elements and that deficiency of this fluid, by reducing the activity of the nutritional processes, gave rise to acromegaly: further evidence that the tie between the nervous system and these organs is sufficiently marked clinically to have attracted considerable attention. That the various theories adduced also bear upon *nutrition* of the nervous elements is significant as testimony in favor of our view. Indeed, the clinical signs that point to impaired nervous action are numerous, and are present in practically all cases of acromegaly when the anterior lobe has become sufficiently enlarged or functionally disordered to involve the posterior lobe, either directly by pressure, continuity of tissue, etc., or indirectly by overstimulating the adrenals, or,

[15] Collina: Gazzetta degli Osped., Jan. 8, 1899.

in the later stages, by causing insufficiency of these organs. In a previous chapter we have—and correctly we now see—ascribed to overactivity of the adrenals the stage of "erethism," and to insufficiency of these glands that of "cachexia." But, if we ask *how* these states are produced by the adrenals, the answer which would not have been available before now seems to be within our reach.

We have previously referred to the vicious circle that obtains in acromegaly. Though primarily located in the anterior pituitary, the lesion probably gives rise to no untoward symptom until well advanced: *i.e.*, until pressure occurs either upon its own structure by the pathological elements or upon the posterior pituitary. Even slight pressure upon the whole organ, as shown by de Cyon,[16] gives rise to typical suprarenal symptoms. But if the posterior pituitary is also considered as a factor in the production of the symptomatic phenomena, as a source of nervous energy, we not only have the vascular erethism of suprarenal overactivity, but distinct evidence of *nervous* erethism besides. This is well illustrated by the following *quoted* lines, *i.e.*, Gauthier's definition of the erethic stage of acromegaly as given by Hinsdale[17]: "The phenomena of *erethism* which characterizes the *first stage* embraces, first, a painful *hyperæsthesia*, which manifests itself in headaches and rheumatic pains; second, an hypertrophy of the muscular fibers which may give to patients a muscular power greater than usual; third, palpitation of the heart accompanying the hypertrophy of that organ; and, finally, the polyphagia and polyuria which may be considered to be connected with an erethic state of the respective organs." Everything here points to overactivity. But these are only the milder manifestations. Tamburini, for instance, describes a case in which "the mental symptoms, on account of which the patient was sent to the asylum, began to show themselves only a year before her admission. They consisted chiefly in delusions of suspicion accompanied by threats and acts of violence. The patient presented, in a marked degree, the bodily changes characteristic of acromegaly. While in the asylum she was confused, resistive,

[16] De Cyon: Archives de Physiologie, July, 1898.
[17] Hinsdale: *Loc. cit.*, p. 30.

and suicidal, and refused her food. . . . Only the anterior lobe was involved, the posterior presenting no change either in volume or structure." This typifies the irritability or stimulation induced by pressure without organic change.

The phenomena produced are of another kind when both organs are involved in the morbid process, as appears to be the case in the following instance reported by Johnston and Monro[18]: The patient, a woman, "was taciturn and intellectually obtuse, and her memory was bad. Her utterance was thick and indistinct, as if her tongue were too big for her mouth. Her gait was slow and shuffling; her expression partly melancholic, partly demented. . . . The skin of the face is of a dull-yellowish tint; the mucous surfaces are pale. . . . Hearing is somewhat impaired. Reflexes are diminished. The subject of these notes remained in hospital for about four weeks. She scarcely ever spoke, took no interest in anything, and slept about sixteen hours daily. . . . She was readmitted in September—blind, more deaf, more drowsy, very feeble in muscular power. She could no longer rise without assistance. Control over the sphincters was lost. . . . Paralyzed. For a couple of months before death there was a discharge of clear fluid from the nose. . . . The pituitary body is represented by a large, red mass, almost diffluent—much softer than brain-substance." The entire organ being destroyed, the posterior lobe had obviously followed the fate of its mate.

In a case described by Pirie[19] the history of the nervous symptoms is very clearly defined, though the author was unfortunately unable to obtain an autopsy. "The disease first manifested itself in 1886, when menstruation finally ceased. Pains and paræsthesia of the arms and legs were felt, and the patient noticed that her hands and feet were getting larger and more awkward. . . . Along with the development of physical symptoms a peculiar alteration of mental condition took place. Attacks of narcolepsy overcame her, she became sluggish and irritable, and she suffered much from the *ennui* of life. . . . Breathlessness on the slightest exertion ap-

[18] Johnston and Monro: Glasgow Medical Journal, August, 1898.
[19] Pirie: London Lancet, Oct. 5, 1901.

peared, and ultimately the muscle weariness so gained upon her that she had to take entirely to bed. . . . Sensory disturbances are marked. Shooting pains in combination with paræsthesia, tingling, and numbness are complained of in the arms and legs. Neuralgic pains are felt also in various parts of the body, viz.: the face, chest, back, and loins. A remarkable perversion of thermic sensibility is found in the lower limbs and over the front of the abdomen and chest up to about the level of the fourth rib, the patient having no sensation of heat in these regions. . . . Sternberg remarks particularly on the occurrence of pain and paræsthesia as valuable signs for diagnosis in the early stages of the disease; they are probably due, he considers, to changes in the cutaneous nerves."

In a previous chapter we said: "Whether the mental symptoms are ascribable to the cerebral hyperæmia or to the impairment of certain functions of the pituitary itself, or to both, it is as yet impossible to say." It now seems evident that *both* organs are involved in the pathogenic process. If the far-reaching meaning of this fact is freely grasped, it seems clear that there lies hidden under the whole fabric—of which we only now see the outline—a truth of overwhelming importance to we physicians: *i.e.*, the fact that it is not only *in acromegaly that the typical signs of impaired function of the posterior pituitary shows itself, but in all syndromes directly ascribable to the suprarenal system: i.e., myxœdema, cretinism, exophthalmic goiter, and Addison's disease, which include in their aggregate the majority of organic changes of a morbid kind to which the system is liable.*

This may be briefly illustrated by further quotations from Dr. Pirie's excellent paper, entirely devoted to the one case. As regards the *muscular system,* the author states that "muscular atrophy is a prominent feature, affecting the thenar, hypothenar, and interossei muscles of the hands, the forearm- and arm- muscles, the calf- and thigh- muscles, and also the glutei," and refers to Duchesnau,[20] "who has made a special study of the atrophy of muscles in acromegaly. So marked is it in some cases that it has been mistaken for syringomyelia,

[20] Duchesnau: Thèse de Lyon, 1891.

progressive muscular atrophy, or amyotrophic lateral sclerosis; it has also been mistaken for Charcot's cervical pachymeningitis hypertrophica and for erythromelalgia." Referring to the *skin*, Pirie says: "Its chromatogenous functions are disturbed, much as in rheumatoid arthritis. Small freckles are frequent; patches of a yellowish bronzing occur also on the face, the chest, and the insides of the thighs. (Motais describes a bronzing such as occurs in Addison's disease.) Numerous small warts are present. (Mollusca fibrosa are described in many cases and xanthoma-like tumors by Dallemagne.) The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse and stands straight upward. There is a scanty beard and moustache. Profuse perspirations are constantly complained of. The heart is dilated. There is tachycardia, the heart beating about 98 to the minute. A soft, systolic, basic murmur is heard at times. Palpitations and fainting fits occur very often. Dyspnœa is marked, and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath." . . . "The *soft parts* are remarkably changed as well *as the bones*. The scalp is much thickened, as is also the skin of the face. . . . In addition to the kyphosis there is a compensatory lumbar lordosis and also a certain degree of scoliosis. The clavicles are enormously hypertrophied. The ribs are thickened and expanded, the costal cartilages feel bony, and there are nodular projections resembling the 'rachitic chaplet' at the junctions of the ribs and their cartilages." . . . "With regard to the *organs of special senses*, the skin of the eyelids is thickened and puffy. The lacrymal glands are hypertrophied. Increased lacrymation occurs at times, and I have noticed a colloid-like secretion between the eyelids." . . . "There is amblyopia, nearly complete in the left eye, and color-vision for blues and yellows is defective. Bitemporal hemianopsia is present. The pupils contract in accommodation and react to light, though very sluggishly in the case of the left eye. With the ophthalmoscope optic atrophy is found." . . . "She suffered much at this time from polydipsia and *glycosuria*, and for over twelve months there was an almost constant dribbling of saliva from the mouth. . . . The

thyroid was greatly enlarged, but under treatment with thyroid substance it diminished much in size." We have seen how dependent the organism is upon the integrity of the suprarenal system when infectious diseases develop.

We can fully agree with Harlow Brooks[21] when he says: "It is quite natural to expect pronounced abnormalities in the various portions of the nervous system in a disease which exhibits so many neurological symptoms"; and his statement that "examinations of the nerve-tissues have shown quite *extensive* and *general* changes" further sustains our deductions. Evidence of this kind, garnered from all sides long before the feature it serves to support is thought of, appears to us of the strongest kind. We again prefer to use the author's own words, therefore, rather than our own, when he reviews the pathology of the disease, and which seems to us to portray *in parvo* the main landmarks of neurological pathology. We have only omitted those of the author's own estimates that do not bear directly upon our subject and what text was not purely descriptive:—

"*Peripheral Nerves.*—The trunks of the peripheral nerves are, for the most part, enlarged; this is directly due to an increase in the connective tissue of the endoneurium and perineurium. Often the sheaths of the nerve-trunks also show considerable thickening. This general connective-tissue hyperplasia frequently so encroaches on the nerve-fibers as to destroy them, and degenerated nerve-fibers are quite commonly found some of which may show complete axis-cylinder destruction (Arnold, Comini). These conditions may persist throughout the entire nerve-trunk, extending even into the nerve-roots. (Arnold, Duchesneau.)

"*Ganglia.*—In the posterior-root ganglia, also, we find the connective-tissue elements greatly increased, so that even macroscopically the ganglia are often considerably enlarged. Microscopically the ganglionic cells are sometimes pressed upon and atrophied (Marie, Marinesco). Arnold reports that he found vacuoles in the nerve-cells. In Cases I and II of the author's, the alterations in the ganglion-cells were slight.

[21] Harlow Brooks: Archives of Neurology and Psychopathology, vol. i, No. 4, 1898, p. 592.

"It is difficult to determine whether the nerve-cell lesions are secondary, perhaps directly dependent on the connective-tissue hyperplasia about the cells and fibers, or are primarily due to defective nutrition of the ganglion-cell bodies. Perhaps these ganglionic changes are wholly, or in greater part, responsible for the degenerations and atrophies which take place in the muscles of the voluntary system.

"*Sympathetic Ganglia.*—The changes in the sympathetic ganglia and trunks have been made the subject of special study by several very prominent investigators, among whom are Marie, Marinesco, and Arnold, and have been looked upon by many as factors of an etiological nature. Finding, as we do, such pronounced change in the blood-vessels, it does not seem at all strange that lesions in the sympathetic ganglia should be present; but a view intimating a dependence or relation of the vascular changes to the lesions in the sympathetic system is not in accordance with our own ideas expressed at the close of this paragraph. In general, the changes in the sympathetic ganglia are very similar to those already described in the ganglia and trunks of the cerebro-spinal system. In some cases the size of the ganglia is considerably increased (Arnold, Marie, Marinesco), and, microscopically, the connective-tissue web is thickened and proliferating. The ganglion-cells are often reported as exhibiting evidences of degeneration." . . . "Arnold has found vacuolization; not infrequently considerable deposits of pigment are seen within the cytoplasm. But, as in Case II, the ganglion-cells may be normal; the Nissl bodies are present in normal arrangement, volume, and shape, and show no deviations in their staining reactions; and the pigmentary deposit is not abnormally abundant. The sympathetic ganglia in the case reported by Gauthier were also normal. It is advisable, at this point, to call attention to the fact that the interstitial hyperplasia is by no means a lesion characteristic of the sympathetic system, but is simply an extension of the general process so often alluded to. The growth of connective tissue in the sympathetic may depend in part on lesions in the walls of the vessels; or both may be referable to the common factor of deranged nutrition.

"*Cord and Medulla.*—The pathological findings in both

the cord and medulla differ greatly. Virchow, and also Fritsche and Klebs, have reported hypertrophy of the medulla. The spinal cord was enlarged in the case reported by Linsmayer. Many observers have reported various degenerations in the cord. Baruch's case was associated with symptoms of syringomyelia; Debierre gives a case with diseased posterior columns, while Arnold, Dallemagne, and Tamburini have found at autopsy irregular degenerated areas in the cord, affecting, however, no special place with any degree of constancy. Usually, as in the first two cases reported in this paper, no abnormalities of either the medulla or cord are found.

"*Brain.*—No constant changes are found in the brain, but, as is the case with every other organ of the body in acromegalia, the encephalon may be enlarged (Fritsche, Klebs, Halsti), though the increase is rarely proportionately as great as that of the body. Usually few microscopical changes of note are found. Demonstrable cytological degenerations are absent, though interstitial and vascular lesions are sometimes reported." This paragraph appears to us to add further testimony to the teachings of experimental physiology which tend to isolate the hemispheres from the true neural tract.

The nature of the process through which the nervous energy liberated by the posterior pituitary affects nervous structures suggests itself as the next subject to receive attention.

THE HISTOLOGY AND PHYSIOLOGICAL CHEMISTRY OF THE NEURON.

We are first brought to inquire into the relationship between the modern conception of the structural composition of the cerebro-spinal axis and the views we have submitted. Granted, therefore, that the posterior pituitary body is the seat of a process through which chemical energy is converted into nervous energy, and that this constitutes the nervous impulses which the cerebro-spinal axis transmits to the various organs, how do the nerve-elements utilize this energy when functionally active?

We refer, of course, to Waldeyer's neuron as the morphological unit of the cerebro-spinal axis, and the processes of

which are not in contact, but sufficiently close, one to the other, as to make it possible, when required, for a nerve-impulse to cross the interval between them. These facts have been satisfactorily established by modern methods, especially through the labors of Golgi and Ramón y Cajal. But the manner in which the gap between the processes is closed—*i.e.*, how the impulse passes from the terminal brush of the axon of one nervous element to the dendrites of the next—is still to be determined. It has been suggested, however, that the processes behave, in a limited manner, as do the pseudopodia of the amœba, and that by a slight extension the interval between the processes is closed. When the processes are not in contact they are said to be in a state of "retraction." Much as such a function would facilitate and shorten our analytical work could incontrovertible experimental facts be adduced to sustain it, we are brought, by a review of the literature of the subject, to recognize that such facts are not available. Indeed, the majority of physiologists and neuro-histologists now consider the question of "amœboid movements of the neuron" in the light of a working hypothesis.

There is one feature of the investigations in this direction which may serve to throw more light upon the whole question if one of the more prominent deductions submitted by us in the present work is taken into consideration: *i.e.*, the fact that *all drugs* cause overactivity or insufficiency of the adrenals.

Much of the physiological work done in connection with the neuron includes the administration of various toxics,—strychnine, chloroform, morphine, etc.,—and amœboid movements or other active manifestations of the protoplasmic processes are thus ascribed to the action of the drugs upon the neurons *per se*, whereas, in the light of our views, the changes of form witnessed should be ascribed to increased or reduced blood-supply when toxic doses are given. To illustrate our meaning we will give in outline an experiment which represents one of the key-stones of the entire theory, that of Demoor. Before doing this, however, it may, perhaps, be well to state that we will consider the terms "*neuron*" as applying to the complete nerve-cell, including processes; "*neuraxon*"

to the (usually) single and long process which extends along the center of the nerve-fiber, and is then called "axis-cylinder; "*dendrites*" to the cell's many processes—some of which end in many branches or tufts—other than the neuraxon. With Foster and Sherrington we will consider that neuraxons carry impulses *away* from the cell, while dendrites transmit impulses *into* the cell. Two other prominent morphological features are the "*gemmules*"—minute projections all along the dendrites—and their terminal twigs, which recall those on the stems of the moss-rose, and the *varicose*, or irregular, swellings that may be observed in the course of the dendrites or their terminal twigs.

The experiment of Demoor was briefly as follows: He *killed* a dog by injections of morphine; a second dog was given morphine for some time, then killed by cutting the medulla; a third was trephined. The next day a piece of the left hemisphere of the latter dog was removed; the animal being then morphinized, another piece—but of the right hemisphere this time—was removed. Portions of the hemispheres of the two killed dogs having also been removed, all specimens were treated in precisely the same manner. The cellular changes were found to be similar in all specimens taken from the morphinized animals: their gemmules had disappeared. Alone of the series the piece removed before morphine had been given was covered with regularly distributed gemmules. Now the fact we wish to emphasize is this: while this experiment is thought by its author to show that the retraction of the gemmules constitutes the inactive state, as induced by morphine through the *local* action this drug is now thought to have upon nerve-cells, the *retraction of the gemmules*, as we view the experimental result, *is due to the suprarenal insufficiency* (total arrest of function in the dog killed with morphine) produced by the toxic. And this is an important feature, since we thus have, instead of a purely local effect, an example of the general physiological process through which the neuron passes from the active to the passive state—provided the histological picture is not a misleading one.

Again, the same structures treated by different methods have been found to yield different results. Thus, H. H. Baw-

den[22] found that "all material treated according to the slow method of Golgi shows, as a rule, an almost absolute freedom from varicosities; varicose cells occasionally occur." The mixed method and the rapid were found to yield practically the same results when the dendrites had taken the stain: the gemmules were almost invariably present and regular. In some sections almost every dendrite was varicose; in others hardly any. All these results were similar whether normal or "toxic" material was used, and the author concludes that "it is impossible for an unprejudiced observer to differentiate or distinguish between the two kinds of material." Lugaro,[23] who has upheld the retraction theory, also reached the conclusion that "imperfect fixation is very largely, though not entirely, responsible for the formation of varicosities and the disappearance of gemmules." Weil and Frank summarize what a review of the literature of the subject shows, when they say: "The findings have been in almost every case positive, although there are occasionally records of negative results and even contradictions,—as, for example, between the investigations of Demoor and of Soukhanoff on the effects of chloroform. . . . Retraction of the gemmulæ and coincident swelling of the dendrites form the essential features of every description."

Judging from the foregoing estimates as to the effects of stains upon dendrites, these phenomena are to be considered as artifacts: *i.e.*, as artificially produced changes. Under these conditions, it is clear that the latter should appear, irrespective of the condition of the animal at the time of its death: *i.e.*, whether under the influence of toxics as stated, fatigue, etc.

That prevailing views in this connection are erroneous is our firm belief after a critical analysis of available experimental evidence. Particularly instructive and valuable in this connection are the experiments of H. H. Goddard,[24] which consisted "in cutting through the entire head of the animal at a single blow with a very thin sharp knife, the parts of the head falling instantly into large dishes of Cox's solution warmed

[22] H. H. Bawden: Journal of Comparative Neurology, May, 1900.
[23] Lugaro: Rivista di patol. nerv. e ment., vol. iii, 1898.
[24] H. H. Goddard: Jour. of Compar. Neurol., Nov., 1898.

to 39° C. In his first experiment, puppies about seven weeks old, sisters from the same litter were used, the one while somewhat tired, the other after having slept. A careful count of the pyramidal cells of the cortex of the somewhat fatigued puppy gave a proportion of 31.1 per cent. of cells showing varicosity, while cells from the same region of the puppy killed after sleeping was 8.5 per cent. In the former animal 15.9 per cent. of the cells showed much varicosity; in the latter only 0.8 per cent. showed a similar state. In the second experiment the first of two sisters was killed on waking in the morning; the second at night when tired and very sleepy. While it "was difficult to find a single varicosity on the dendrites of the morning puppy, for long distances in the cortex of the evening puppy" it was difficult to find a cell "whose processes" were "not more or less varicose." It is evident that in these instances at least the stain was not alone the source of varicosities, since it was only in the tired puppies that the varicosities were very marked, while in the thoroughly rested animal practically none could be found.

Judging from these experiments, varicosity of the dendrites coincides with a fatigued condition. This corresponds exactly with the experiment of Demoor, previously described, since retraction of the gemmules is accompanied by varicosity; so that fatigue and a large dose of morphine must have produced similar results.

If the staining process alone caused the formation of varicosities in Demoor's experiments,—the same method having been used for all specimens,—how is it that one of the latter showed gemmules (which means absence of varicosities), and that this solitary specimen is precisely from the only animal which had not received morphine? Berkley[25] found that poisoning with alcohol "in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum" very similar in character to the pathological lesions produced by other more virulent soluble poisons. The terminal twigs of the dendrites were also found to have become varicose

[25] Berkley: Brain, Winter, 1895; and Johns Hopkins Hospital Reports, vol. vi, 1897.

or beaded, the gemmules being very scarce or absent. Here, again, is a condition which, as does fatigue, morphine, and, we may add, chloroform, chloral hydrate, and other toxics used by Demoor and others with similar results, all tend in the one direction: *i.e.*, to morbidly reduce functional activity. This is a well-known characteristic of the bromides. In a study of the cortical cells under the influence of poisonous doses of potassium bromide, H. K. Wright[26] says: "If the primal ascending dendron is followed to its visible termination, several ampullous or varicose swellings of varying size are met with," . . . "on the basal processes also varicosities are to be seen; but they are small and, like those of the ascending protoplasmic process, are sharp in outline, and shorn of the lateral projections which obtain on the unaltered part of the extensions. One may be seen on each secondary branch, and ranges in size from a small and *scarcely recognizable* to a *readily obvious* swelling. None of them, however, reach the dimensions of the apical projection and its branches."

If the method of staining is the cause of all this, we are brought to the conclusion that it must be selective as to the parts of the dendrite it affects, and that only functionally-impaired cells are so affected by the stain as to show varicosities. Even then staining methods would furnish precious indications. But it seems clear to us that, while the newer chrome-silver methods still furnish imperfect pictures of the morbid alterations of the neuron, they cannot with justice be said to either cause or prevent the formation or disappearance of gemmules and varicosities; in other words, that they are not artifacts of the Golgi method. The marked tendency of the swellings to locate at the apices, and the gradual reduction of the varices as the cell-body is approached recall, on the other hand, a well-known pathological principle: *i.e.*, that the morbid effects of impaired general nutrition are first felt by terminal structures.

And the painstaking experiments of Weil and Frank do not appear to us in the least to prove their conclusions that "the varicosities must be regarded as artifacts" and that "they

[26] H. K. Wright: Brain, Summer, 1898.

depend for their presence and their amount on the form and method made use of." Demoor employed the same method in each of his *comparative* experiments and his results were not similar, the non-morphinized specimen alone differing from all others. Hubbard used the identical method in both his *comparative* experiments, and likewise obtained results which distinctly showed a marked difference between the rested and fatigued animals. In these and other experiments referred to, the pathogenic agency, including fatigue, was allowed sufficient time to produce alterations in the cortical cells, if *nutrition* has anything to do with the process.

In Weil and Frank's experiments the animals were overwhelmed by the quantity of toxic administered, and death occurred—if our views are sound—by arrest of the adrenocardiac functions, long before any *marked* action upon the cells could possibly have occurred. The doses of morphine administered were 0.38 and 0.41 gramme (6 and 7 grains), respectively, with death in 15 minutes; of strychnine nitrate, 0.018 gramme ($^1/_3$ grain), death in 20 minutes; of hypertoxic urine, 125 to 150 cubic centimeters (4 to 5 ounces), death in 15 to 25 minutes. That these are overwhelming doses in rabbits is evident. One animal was killed with serum (30 cubic centimeters—1 ounce) in 5 minutes; others with chloroform inhalations in 10 minutes; one by tracheal clamping in 8 minutes. The rest, six animals, were destroyed instantly by instrumental procedures. In none of these animals was there any distinction established as to whether they had been sleeping, eating, or romping, etc. That some were old and others young in the series of nineteen is probable; as is well known, erethism, especially in such delicate structures, is greatly influenced by age, and a few months in the rabbit represent as many decades in man. The weight of each animal was not recorded in order to establish the relative action of a given dose of the toxic used per pound of animal, though, of course, in the experiments, the large doses used precluded any usefulness on this score.

Finally, the authors themselves will surely admit that "no varicosities," "varicosities," "slightly varicose," and "very slightly varicose," the method of notation utilized by them,

conveys but little exact information. And still, even this sustains a deduction opposite to theirs. Indeed, the short period of time that elapsed between the injection of the toxics in the animals killed in this manner—represented by 108 blocks of slides—must have sufficed to initiate retraction of the gemmules and the formation of varicosities, since only 10.2 per cent. of these blocks show no varicosities. When, on the other hand, the proportion of animals killed instantly by instrumental procedures—93 blocks of slides—is analyzed, over two and a half times as many, *i.e.*, 28 per cent., are found to show *no* varicosities.

But a fair question suggests itself in this connection: Why do the remaining 72 per cent. show any varicosities? Only 14 per cent. of the blocks from the instantly killed animals are recorded as "varicose," the remaining 58 per cent. being entered as "slightly" or "very slightly" varicose. In their explanation of the scope given these terms, the first means "at least some varicosities" and the second as "only very few varicosities." Now, the authors state that "in the first nine cases here recorded the brains were placed in fixing fluids within three to five minutes." Nothing is said of the rest; so that we may infer that the ten other brains were immersed after longer intervals. We have previously seen, when the conversion of myosinogen into myosin was studied, that oxidation processes continued even after death: *i.e.*, until all the oxygen had been utilized. That this must be the case with the brain, which contains one-fifth of the blood of the whole body, and that products of metabolism, especially CO_2, should form in the entire encephalon is evident. It normally follows that we have in this factor a potent cause for the retraction of gemmules and the formation of varicosities.

Indeed, the contrast between the results reached speaks for itself when compared to those of Goddard, who resorted to procedures in which the exact condition at the instant of death were preserved, "the parts of the head falling *instantly* into large culture dishes warmed to 39° C." Even continuation of the normal brain temperature was insured. And what were Goddard's results? "It was difficult to find a single varicosity on the dendrites of the morning puppy,"—*i.e.*, the thor-

oughly *rested* animal; while in the thoroughly *tired* one "for long distances in the cortex . . . it is difficult to find a cell whose processes are not more or less varicose." That fatigue is the result of an accumulation of products of metabolism and especially CO_2 is generally recognized.

Goddard's procedure appears to us to represent as nearly perfect a one as available staining methods (Cox's and the rapid method show considerable parallelism in Weil and Frank's report, while the mixed and slow methods appear unreliable and contradictory) will allow; and *his results, in our opinion, portray the actual changes that are produced in the neuron under the influence of poisons of any kind and during sleep: i.e., when the blood-supply of the brain is reduced.*[27]

Weil and Frank state that they "are able fully to corroborate the statement of Cajal that normal and toxic material cannot be differentiated by the number of varicosities or of gemmules." The care with which such experiments must be conducted, apart from the method of staining adopted; the need of immediate immersion, and other details to which we have referred, invalidate any opinion that the distinguished Spanish histologist may have expressed on this score, unless he can show that his experimental *physiological* procedures were as perfect as his staining work must have been. Indeed, we must express the belief that the greater part of the physio-histological work done so far in this connection is valueless owing to the absence of the precautions to which we refer.

Again, Ramón y Cajal's conclusions that "the nerve-cells do not move, but, on the other hand, that the neuroglia-cells do move" (which underlies his view as to the gemmules and varicosities showing no difference when normal or "toxic"), has been shown by Dercum to embody its own refutation. "Cajal," says the latter author, "points out the fact that the processes of the neuroglia-cells have numerous short arbores-

[27] We wish to particularly emphasize the fact that we are in no way criticising adversely the work of Drs. Weil and Frank. We have nothing but praise to express for these investigators. Much of the searching inquiry to which we are submitting their paper includes the use of features introduced for the first time in the present work, and obviously unknown to them. Indeed, if our views eventually prove to be sound, we will owe much to the counter-evidence Drs. Weil and Frank—and, we may add, Dr. H. Heath Bawden—have published.—S.

cent and plumed collaterals, and he states that in these cells two different phases can be observed: first, a stage of contraction,—that is, a stage in which the cell-processes become shortened; and, secondly, a stage in which the cell is relaxed,—that is, a stage in which the processes of the neuroglia-cells are elongated. He maintains that the processes of the neuroglia-cells represent an insulating and non-conducting material, and that during the stage of relaxation these processes penetrate between the arborizations of the nerve-cells and their protoplasmic processes, and so make difficult or impossible the passage of the nerve-currents; on the other hand, in the stage of contraction the processes of the neuroglia-cells are retracted, and they no longer separate the processes of the nerve-cells, and the latter are thus *permitted to come into contact.*[28] Evidently Ramón y Cajal admits the very thing against which he contends, for if the nerve-cell processes are at one time not in contact and at another are in contact, they must certainly move, and the question before us is self-admitted. It matters not whether the processes of the nerve-cells move little or much, but that they move at all is the question at issue, and this Ramón y Cajal admits, though he makes the movement a purely passive one."[29] To us it appears clear that, since Ramón y Cajal held the nerve-cell to be a passive structure, requiring an independent connecting-link to close the circuit with the adjoining cell, he must have denied both the gemmules and the varicosities any physiological importance. His opinion, therefore, that normal material cannot be differentiated from toxic material, when applied to the retraction of gemmules and the formation of varicosities, cannot be said to rest upon solid premises, and, for the time being at least, to in no wise affect the question.

In a comprehensive review of the anatomy and physiology of the nervous system, L. F. Barker[30] makes the following remarks: "The physiologist of the present day sees in the func-

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[28] We will see farther on that Cajal's observation as to the relaxation and contraction of neuroglia-cell processes is valuable in that it proves that the tips of the gemmules do not transmit nervous energy.—S.

[29] Dercum: University Medical Magazine, April, 1897.

[30] L. F. Barker: New York Medical Journal, May 15 *et seq.*, 1897-98.

tions of the nervous system, even in those which are most complicated, only certain manifestations of energy. Moreover, he believes that in neurons, as in all other cells of the body and as in the world generally, the law of the conservation of energy during transformation holds, and consequently regards the phenomena of irritability, as exhibited by a neuron or by groups of neurons, as the kinetic representative of the potential forces of the cells and their foodstuffs. The metabolic activities and the vital manifestations of the cell are concomitant processes—another example of the inseparable connection which exists between what we term matter and energy. There has been in many quarters a certain amount of hesitancy in accepting the view that the capacities of the nervous system, particularly those of the brain, are dependent directly upon the chemical and physical alterations which are continually going on within its constituents: a hesitancy which, though it has in the past proved a serious obstacle to progress, is happily now fast disappearing. For the plant, all the evidence goes to prove that under the influence of sunlight and heat marked chemical and physical changes take place within it which we recognize in its vital processes. In the animal—be it granivorous, carnivorous, or, like man, omnivorous—it is the chemical energy introduced as food which represents, in the main, the source of the energy of the organism. . . . The physiologists have been struggling for fifty years or more to gain an insight into the nature of what they call nerve-impulses, by which is to be understood the occurrences inside axons: for example, at the time when we have good reason to believe that they are functionally extraordinarily active. Their efforts have supplied us with a multitude of data, physical and chemical, interesting enough, no doubt, but which can serve as only the barest prolegomena to an explanation of the essence of the occurrences. If we are so badly informed concerning these elementary and fundamental phenomena we may very well be content to be modest for some time to come in our claims as regards a physiological psychology. It is by no means impossible that in the nervous system forms of energy are concerned which do not exist outside the animal body and which yet remain to be recognized and studied. . . .

Truly, to find out the properties of a single neuron would be a task appalling enough; but, when we remember that of the millions of neurons in one individual perhaps no two are just alike, the quest would seem hopeless. But instead of burying ourselves in pessimistic reflections, or being discouraged by what is at present unattainable, by what may perhaps forever remain to us unknowable, we may profitably turn to the consideration of some of the points which lie more within our ken. One point, self-evident enough when one's attention is directed to it, but which often appears to have been overlooked in connection with the neurons, is the unremitting character of their activity. With a metabolism as complicated as that occurring within the nerve-units it is inconceivable that there can be any period in which alterations in chemical structure, and consequently energy transformation, are not going on. From moment to moment, throughout all the hours of the day and night, analytical and synthetic processes are taking place, associated with the alterations in physical forces which necessarily accompany these changes. In common with everything that lives, the neurons know no absolute repose. As I have said, in speaking of their metabolism, periods of extravagant activity may alternate with periods of more economic change, but total rest is inconsonant with continuance of existence. We are forced to believe that what we ordinarily speak of as the passage of a nerve-impulse represents, as it were, *a stormy process in the nerve-fiber*, and that just as absence of a storm does not mean absence of weather, there are in all probability minor alterations—currents, if you will—passing to or fro or *passing to and fro in a given nerve-fiber in the intervals* between the more violent excitations."

The words that we have italicized will doubtless recall some of the more prominent features previously emphasized in respect to the relative nervous processes involved in the functions of the various organs reviewed. We have termed "passive" that form of energy continuously transmitted to tissues and vessel-walls. A quiet and steady flow of blood into the cellular structures, sustained by the tonic contraction of the arteries, and a stream of nervous impulses to the tissues coinciding in rhythm, perhaps, with that sent to the vessels,

suffice to insure nutrition and to hold the structures thus supplied ready for active work. What is the source of *this* energy?

If the posterior pituitary reinforces the flux of impulses when functional activity is demanded, passive energy would seem to require another source, and as the lower, or middle, brain and the cord are included in the "sphere of influence" of this organ, the hemispheres are the only parts of the encephalon that can supply the need. But they do not. Removal of the hemispheres, we have seen, does not impair muscular activity; a frog can jump, a pigeon can fly, etc., and, after a short period of shock-paralysis immediately after the operations, movements return: evidence that their nutritional metabolism, incited and regulated by nervous impulses, continues. Evidently, therefore, the hemispheres have nothing to do with the process; they are solely the seat of the "mind," and constitute an organ among the rest, itself supplied with vasomotor nerves (Obersteiner, Gulland, Huber, Hürthle, Cavazzani, François-Franck, *et al.*), and probably with its own nutritional nerve-system. We are, therefore, brought back to the posterior pituitary as the only organ capable of satisfying the needs of the situation: *i.e.*, as the only source of passive energy.

This suggests that metabolism may suffice, through the agency of the blood's oxidizing substance, to sustain physiological activity during the intervals between "stormy processes of the nerve-fiber"; but this is promptly shown to be a wrong interpretation when the effects of section below the medulla are recalled. As all the arteries of the organism are immediately relaxed, a continuous stream of impulses must have served to hold the vessels in tonic contraction: evidence that passive nervous energy is a factor to be reckoned with. Thus, the fact that all co-ordinated muscular movements continue after removal of the hemispheres relegates to the middle brain the function of supplying active energy—and, obviously, passive energy likewise, the need of the latter being shown by division of the medulla. Indeed, *passive* energy may well be described as passing to and fro in a given nerve-fiber in the intervals between the more violent excitations, while *active* energy can as fittingly be likened to "a stormy process in the

nerve-fiber": both ascribable, it now seems likely, to the one organ, the posterior pituitary body.

To establish the functions of the posterior pituitary within its proper physiological limits, however, it is necessary to ascertain how nervous elements in general and neurons in particular are nourished, since it is upon the degree of perfection with which the nutritive processes are carried on by the blood that the functional integrity of these structures depends.

The fact that a *general* nutritional process prevails, of which the suprarenal system is the primary motive agency, we have shown; but it finds further support in the following statements of Professor Barker's—which, of course, but emphasize a generally known fact—that, "in the absence of substances in the body derived from the thyroid gland, the nervous system undergoes very important and serious metabolic modifications, evidenced by the remarkable nervous and mental phenomena with which all are now familiar. On restoring these substances to the body by the administration of a thyroid extract the symptoms may sometimes be made to disappear. It is likely, however, that the neurons find their staple foods in the main nutritive constituents of the blood as derived from the food digested in the stomach and intestines and purified by the lymph-glands and liver."

We have, we believe, satisfactorily shown that the thyroid secretion sustained the activity of the anterior pituitary body, and therefore of the entire suprarenal system, by pouring its secretion—thyro-iodine perhaps—into the blood. The functions of the digestive organs we have also reviewed. Among the latter, however, are two upon which we laid considerable stress,—*i.e.*, the spleen and pancreas,—and we called attention to the great importance of trypsin—the splenopancreatic ferment—in the conversion of albuminoid substances, and especially of their toxic derivatives, into benign products. These albuminoid substances, we have seen, then pass through the liver, and, after traversing the cardio-pulmonary circuit, are distributed broadcast throughout the organism. There is a feature which we kept in abeyance, however,—though a well-known one,—since at the time its true weight would not have asserted itself: *i.e.*, the fact that *albuminoids*

include nucleins derived from the animal and vegetable cells ingested with food, which nucleins contain at least 3 per cent. of phosphorus. We can now realize how great is the physiological rôle of the pancreas and of the spleen in the organism.

Indeed, the functions of these two organs may be said to constitute one of the pillars upon which the vital functions rest. As a constituent of calcium phosphate, phosphorus is found in the bones, teeth, cartilage, and other tissues; in the blood, milk, etc., in quantities which bespeak of its functional prominence, since calcium phosphate is represented by nearly six *pounds* among the organism's constituents. Sodium phosphate—which gives the blood, lymph, and other body-fluids their alkalinity and fluidity, and the potassium and magnesium phosphates, which fulfill much the same rôle, obviously find in phosphorus their main dynamic attributes. But it is when we reach the nervous system that the functional worth of this element reaches its highest mark.

How are nervous structures—neurons, axis-cylinders, sheaths, etc.—adequately supplied with blood-plasma, their oxidizing substance, their phosphorus, etc.?

The Physiological Chemistry of Nerves.—The functions of myelin, or white substance of Schwann—a jelly-like homogeneous and transparent material which surrounds the axis-cylinder of nerves, and is only separated from it by a thin protoplasmic film—may be said to be unknown. It is a fatty substance, blackened by osmic acid, and which, after death, coagulates and becomes opaque, loses its homogeneity, etc. Myelin is now universally considered as a protective coat: a function which the overlying neurilemma already fulfills. Is myelin fatty in the true sense of the word? Examined chemically in quantities, a very large proportion of dried nerve-substance—about one-half, according to some observers—consists of a peculiar body: *cholesterin.* This body is not a fat, but an alcohol; like glycerin, however, which is also an alcohol, it forms compounds with fatty acids. "Though we do not know definitely the chemical condition in which cholesterin exists during life in the medulla," says Professor Foster, "it is more than probable that it exists in some combination with some of the really fatty bodies also present in

the medulla, and not in a free isolated state." . . . "Besides cholesterin, 'white' nervous matter contains a less, but still considerable, quantity of complex fat whose nature is disputed. According to some authorities rather less than half this complex fat consists of a peculiar body, *lecithin,* which we have already seen to be present also in blood-corpuscles and in muscle. Lecithin contains the radical of stearic acid (or of oleic, or of palmitic acid), associated, not—as in ordinary fats—with simple glycerin, but with the more complex glycerin-phosphoric acid, and further combined with a nitrogenous body, *neurin,* an ammonia compound of some considerable complexity; it is therefore of remarkable nature, since, though a fat, it contains both nitrogen and phosphorus." Cholesterin ($C_{26}H_{44}O$), lecithin ($C_{44}H_{90}NPO_9$), and neurin ($C_5H_{15}NO_2$), as shown by the formulæ, are all oxygen-containing bodies. May this supposed coating and insolating material, myelin, not be to the nerve what myosinogen is to muscle?

Cholesterin, we have seen, is associated with hepatic functions. "It is singular," says Professor Foster, "that, besides being present in such large quantities in nervous tissue, and to a small extent in other tissues and in blood, cholesterin is a normal constituent of bile." We have previously referred to the fact that this alcohol, the only one which occurs in the body in a free state, combines with glycocholic acid in the formation of bile, and is thus eliminated by the liver. This view sustains that of Austin Flint, who looked upon cholesterin as an excrementitious product derived from the nervous system: *i.e.,* the result of nerve-metabolism. Cholesterin is present in abundance in the white substance of the cerebro-spinal axis, as well as in the myelin, or white substance of Schwann, in nerves. We have seen, however, that the elimination of excrementitious products by the liver is carried out by the combination of various agencies: mainly glycocholic and taurocholic acids derived from cholic acid through an oxidation process in which the oxidizing substance plays the predominating rôle. That an oxidation process also occurs in a nerve during functional activity is suggested by the following lines of Mathias Duval: "Direct experimentation has shown that the functionating nerve is the seat of *increased combustion;* this

is accompanied by the liberation of heat, the presence of which Schiff has demonstrated even up to the nerve-centers, under the influence of fear, of excitation of the senses, of any cause —in a word—which produces cerebral activity."

Lecithin—"a conspicuous component of the brain, nerves, yelk of egg, semen, pus, white blood-corpuscles, and the electrical organs of the ray"—suggests its identity as at least one of the sources of energy we are seeking by the fact that if merely allowed to stand at the ordinary temperature its solutions acquire an acid reaction and are decomposed. In the intestines it sometimes breaks up into its constituents: fatty acids, glycerin, phosphoric acid, and *cholin* (Howell). Neurin is, in reality, cholin, and therefore a decomposition product of lecithin. As previously stated, Tappeiner[31] obtained fatty acids as a result of cholic-acid oxidation. These facts, of course, are only cited as mere landmarks to indicate that we are dealing with oxidizable bodies. As far as the nerves themselves are concerned, therefore, it seems probable that we have in lecithin an agency capable, by the character of its molecule,—*i.e.*, carbohydrates, phosphorus, etc.,—of acting as a potent source of working energy when brought into contact with the oxidizing substance; and in cholesterin the main waste-product of nerve-catabolism.

Admitting, then, that we have in the lecithin of myelin a body capable of acting as a source of energy in a way similar to myosinogen in muscle, how does the oxidizing substance of the blood-plasma reach it? The nodes of Ranvier and the neurilemma that covers them allows silver stains to reach the axis-cylinder, but the myelin itself does not permit of this. This suggests that the nodes themselves—*i.e.*, the rings forming them—may allow the blood-plasma to filter through them, thus bringing the oxidizing substance in immediate contact with the axis-cylinder. The finer anatomy of nerves indicates that such may be the case. Indeed, the nodes referred to occur at regular intervals, and separate the nerve, as is well known, into as many segments, which recall, in a measure, the muscle-fiber and the liver-cell or, at least, features characteristic of both these structures. If the blood-plasma can penetrate the

[31] Tappeiner: Zeitschrift für Biologie, Bd. xii, S. 60, 1876.

nodes of Ranvier as do stains, there only lies between it and the axis-cylinder an extremely delicate layer of protoplasm,—Mauthner's sheath,—which in no way would impede the entrance of the fluid into the axis-cylinder itself.

The term "cylinder" suggests the tubular shape of the latter: in accordance with Remak's view that it consists of a delicate, longitudinally striated tube, filled with an albuminous liquid. The prevailing view, however, is that of M. Schultz, who considers the axis-cylinder as made up of fibrils united by an intervening unknown substance. This seems to us to vividly recall the arrangement of muscular fibers as regards their relation with the blood-plasma: *i.e.*, minute fibers into which the plasma may freely enter. Again, we must not lose sight of the fact, in this connection, that the axis-cylinder is nothing but the elongated axon of a neuron, and that the fibrillæ now referred to, therefore, represent the intimate structure of a neuron's axon. Now, as Schäfer holds that these fibrillæ are extremely fine tubes filled with fluid, and as the character of this fluid is not known, we have good reason to believe that they are channels for the blood-plasma: *i.e.*, for the oxidizing substance.

But there is another feature which points to the axis-cylinder as a channel for the oxidizing substance: *i.e.*, the fact that the so-called "medullary sheath"—*i.e.*, the myelin itself—contains a supposed "supporting frame-work." The striæ representing them were at first termed "clefts" or "incisures" by Schmidt, Lautermann, and others, but Ranvier considered them as protoplasmic septa which subdivide each internodular segment of the nerve into several conico-cylindrical chambers. W. H. Wynn,[32] who gives an excellent review of this subject and the results of personal researches, refers to those of Rezzonico[33] and Golgi,[34] who "from the examination of fibers treated by a mixture of bichromate of potash and osmic acid, and afterward by nitrate of silver, find that each cleft is occupied by what appears to be a thread of darkly-stained substance passing *spirally around the fiber*. They consider," he

[32] W. H. Wynn: Journal of Anat. and Physiol., April, 1900.

[33] Rezzonico: Archivio per le Sci. med., Torino, vol. iv, 1880; and Gazzetta med. ital. lomb., Milano, vol. i, 1879.

[34] Golgi: Arch. per le Sci. med., Torino, vol. iv, 1880.

adds, "that the supporting frame-work of the sheath consists of *a chain of funnels* surrounding the axis-cylinder, each funnel being formed by a spiral thread." Tizzoni[35] "believes that there is but one net-work closely investing the axis-cylinder, and that it is *in connection with* the slits of Lautermann." McCarthy is stated to have shown that, "after a nerve has been hardened with picric acid and ammonium chromate, the medullary sheath contains minute, rod-like structures, which pass radially between the axis-cylinder and the primitive sheath so as to give the cross-section of a fiber the appearance of a wheel. The rods stain with carmine and hæmatoxylin, which do not stain the myelin. It is not possible to isolate the rods as separate elements, for they are not distinct from one another, but united." Finally he refers to the fact that Lautermann, von Stilling, Roudanowski, and McCarthy all believe that there is "a system of *hollow canals* in the sheath of the axis-cylinder," and himself reaches the conclusion that the cones they form are protoplasmic, and not composed of neuro-keratin, as is usually held. He divides "each cone into six segments placed at regular distances apart and converging from the primitive sheath to the axis-cylinder." This is well shown in the annexed illustration, reproduced from his paper. If we now consider the segments as canaliculi leading from the axis-cylinder, we can readily see how the blood-plasma can penetrate the myelin and its oxidizing substance, and these bodies carry on, when brought into contact, a reaction similar to that which occurs in muscle-fiber. Indeed, if the various features enumerated are collectively considered, it will become apparent that *the myelin, or white substance of Schwann, when in contact with the oxidizing substance of the blood-plasma undergoes a reaction in which chemical energy is liberated.*

When we consider that the axis-cylinder is, as stated, the continuation of a neuron's axon, it is not difficult to account for the various phenomena, known under the general term of "nerve-degeneration,"—*i.e.*, the disorganization of myelin, the dissolution of the myelin, etc.,—at the distal end of a nerve,

[35] Tizzoni: Archivio per le Sci. med., vol. iii, fasc. 1, 1878.

when the latter has been cut. Very suggestive, in this connection, are the following lines by Professor Barker[36]: "Waller proved that if a motor nerve was severed there resulted complete degeneration of the fibers in the peripheral end, even

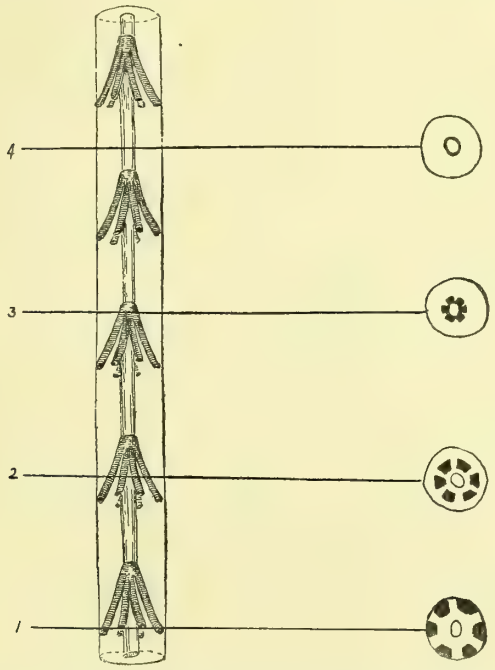


DIAGRAM OF RELATION BETWEEN LONGITUDINAL AND TRANSVERSE SECTIONS, SHOWING CONES CUT ACROSS AT DIFFERENT LEVELS.

1, at base of cone; 2, through middle of cone; 3, through apex of cone; 4, through interval between two cones. In 1, 2, and 3 the cone segments and protoplasmic sheaths are seen. In 4 only the thin protoplasmic sheaths beneath primitive sheath and around axis-cylinder are visible. (*W. H. Wynn.*)

to the muscles which they govern, the central end remaining apparently intact. As a matter of fact, the changes characteristic of the Wallerian degeneration could not, as a rule, be traced farther in the central end than to the first node of Ranvier." Stewart[37] states that "in the degenerated nerve

[36] Barker: *Loc. cit.*, p. 740.
[37] Stewart: "Manual of Physiology," p. 607.

the substances soluble in ether are relatively increased owing, in part, to fatty degeneration of the axis-cylinder," and that "the percentage of phosphorus is markedly diminished (Mott and Barratt)."

Another process which seems to acquire a certain degree of light is nerve-regeneration. It is obvious that if we grant the axis-cylinder, as the extension of the axon, all functional and nutritive attributes, we may easily explain peripheral nerve-degeneration, but not regeneration, the peripheral segment being unprovided for by reason of the section. We know, on the contrary, that a piece of the nerve must be removed in order to prevent reunion, and that otherwise in two or three weeks, and often earlier, its functions will be restored. New cylinders and fibrils grow, acquire myelin, and, perhaps, guided and assisted by (nucleated) neurilemma, soon meet those of the peripheral segment and become connected with them. Physiological functions of a normal kind must underlie this process even in the peripheral end of the nerve; otherwise union would not take place. Finally (we can only refer to a few of the more prominent processes involved in the vast subject now claiming our attention) the functional phenomena that follow after division of the cord distinctly indicate the continuation of nutrition and the functional activity—though impaired—in the distal fragment. Foster, for instance, says: "In the mammal (dog) after division of the spinal cord in the dorsal region regular and apparently spontaneous movements may be observed in the parts governed by the lumbar cord. When the animal has thoroughly recovered from the operation the hind-limbs rarely remain quiet for a long period of time; they move restlessly in various ways; and, when the animal is suspended by the upper part of the body, the pendent hind-limbs are continually being drawn up and let down again with a monotonous rhythmic regularity suggestive of automatic rhythmic discharges from the central mechanisms of the cord. In the newly-born mammal, too, after removal of the brain movements apparently spontaneous in nature are frequently observed. But all these movements, even when most highly developed, are very different from the movements, irregular and variable in their occurrence, though orderly and purposeful

in their character, which we recognize as distinctly voluntary." Indeed, the nervous energy that myelin and the oxidizing substance procure is that which allows a frog deprived of its hemispheres and its middle brain "to sink in water as though the animal were of lead."

The axis-cylinder composed of fibrils into which blood-plasma penetrates being continuous with the axon of a neuron, we are brought to realize the nature of the parallelism between the functional phenomena of the latter and those of the suprarenal glands to which we have already referred. But we must not lose sight of the fact that each "medullated" nerve-fiber is divided by the nodes of Ranvier into as many subdivisions, and that each internodal segment receives its own supply of plasma. Does the neuron receive its supply through this chain of segments, or, rather, through the axis-cylinder that passes through them? That the former mechanism alone prevails is improbable, since so prominent a part of the entire structure as its cell-body, the seat of its nucleus, would hardly be supplied in so indirect a manner. The very importance of its functions betokens the existence of direct supply. Does such a vascular system exist? Fortunately, we have not far to seek.

THE CIRCULATION OF THE NEURON.—Barker, in a review of the facts that have been adduced for or against the neuron doctrine,[38] concludes that "it may be said, with fairness, that the control instituted by hundreds of histologists in various parts of the world has practically in every instance in which the method of Golgi or the method of Ehrlich has been employed gone to confirm the conception that the neuron is a unit in the sense of Waldeyer." The latter investigator's words, giving the gist of his doctrine, are also quoted: "If we review the main advance, made certain by the anatomical investigations discussed, it lies, in my opinion, in the sharper limitation, now possible, of the anatomical as well as the functional elements of the nervous system (for such we have to consider the nerve-units-neurons), and also the discovery of collaterals, with their end-arborizations, by Golgi and S. Ramón y Cajal." The following lines of Waldeyer's are also

[38] Barker: American Journal of Insanity, July, 1898.

quoted: "If we assume, with Golgi and B. Haller, the existence of *nerve net-works*, the conception is somewhat modified, but we can still retain the nerve-units . . ."—all of which tends to show that, while the neuron doctrine stands on a solid foundation, there is a stumbling-block in its way which has not as yet been removed. Especially is this true since the investigations of Apáthy, of Naples, who, after several years' study, has unquestionably demonstrated the existence of a net-work of what he terms "neuro-fibrils."

That Apáthy's "neuro-fibrils" as well as Golgi and Haller's nerve net-works are *not* nerve-elements, but fine capillaries which serve for the circulation of blood-plasma, seems to us probable. In the following extracts the italicized words will serve to call attention to the various links between these structures and others that we have analyzed. Professor Barker summarizes Apáthy's views as follows: "Apáthy has been convinced for some twelve years that the nervous system is composed of two varieties of cellular elements entirely different from each other: nerve-cells and ganglion-cells. The *nerve-cells*, the architecture of which is quite in accord with that of *muscle-cells*, give rise, he thinks, to neuro-fibrils. A neuro-fibril, in turn, passes out *of a process of a nerve-cell* and then goes *through a number of ganglion-cells*, and ultimately, after leaving the last ganglion-cell with which it is connected, passes more or less directly to a muscular fiber or to a sensory cell. The neuro-fibrils are, as *conducting substance* for the nerve-cells, what the *muscle-fibrillæ are as contractile substance for the muscle.* The pathways to be followed by the neuro-fibrils are predestined from the earliest embryonic stages, for they correspond, according to Apáthy, to the *intercellular protoplasmic bridges.*" That we have all required elements in support of our belief is evident; we have seen that muscle-fibers are, in reality, delicate tubes; that vascular channels for the transmission of blood-plasma should be protoplasmic is as obvious as is the need of their penetrating into and out of the cells.

What appears to us as conclusive evidence is indirectly afforded by the deductions of Ehrlich, suggested by his study of the methods of staining living nerve-cells and their processes with methylene-blue. "Ehrlich found," says Barker, "that by

injection of a solution of methylene-blue dissolved in salt solution *intra vitam* into the *blood-vessels* of an animal, the *axis-cylinders* of many of the nerve-fibers (see Fig. 1), as well as numerous (particularly sensory) nerve-endings (see Fig. 2),

FIG. 1.—NERVE-FIBERS FROM A FROG INJECTED WITH METHYLENE-BLUE (METHOD OF EHRLICH). (*After Kölliker.*)

The axis-cylinders are stained dark blue. In places the myelin sheath is somewhat stained. The nodes of Ranvier and the divisions of the fibers at some of the nodes are well shown.

were stained after a time, when exposed to the air, an intense-blue color, the other tissue-elements remaining little or not at all affected." It seems clear that, if a solution introduced through blood-vessels can stain the axis-cylinders, the liquid

within the latter must be more or less a continuation of that in the blood-vessels. Again, we have suggested that the blood-plasma, including its oxidizing substance, was the liquid in the axis-cylinders; that this is true is shown by Ehrlich's observation that "the conditions in the nerve-structures essential to the methylene-blue reaction" were, he thought (1886): "(1) oxygen saturation; (2) alkalinity." We have shown that these are the essential attributes of blood-plasma.

FIG. 2.—SENSORY NERVE-ENDING STAINED WITH METHYLENE-BLUE (METHOD OF EHRLICH) IN THE EXOCARDIUM OF THE LEFT AURICLE OF A GRAY RAT. (*After Smirnow.*)

This seems to us to afford an insight into the physiological chemistry of the axis-cylinder of the neuraxon when a short distance below the latter it has become a medullated nerve. Indeed, the prevailing view that the myelin represents a protective and insulating coat may at least be said to be open to doubt, especially when coupled with the facts that its chemical composition is unknown, and that there is another external coat: the neuro-keratin neurilemma, which suggests, by its composition, that it is an isolating covering and that it also fulfills this

rôle in non-medullated nerves. That the myelin is the seat of a combustion process during which heat is liberated and a decomposition product, cholin, is formed, we have seen. If we now consider the composition of the active component of myelin, lecithin, *i.e.*, carbohydrates and phosphorus, and its analogy, as regards carbohydrates, to myosinogen, the probability that it serves as a source of energy, as does the latter when in contact with oxygen, suggests itself. That such is the case, however, is shown by the fact that the contents of the neuraxon or axis-cylinder fulfills the conditions necessary for methylene-blue staining, as laid down by Ehrlich, *i.e.*, oxygen saturation and alkalinity, the characteristics of blood-plasma. Indeed, it seems to us permissible to conclude that:—

1. Myelin, or the white substance of Schwann, is to nerve-structure what myosinogen is to muscle-fiber: i.e., its immanent source of energy.

2. The axis-cylinder and the canaliculi derived therefrom are made up of fibrils that serve as channels for blood-plasma.

3. A part of this blood-plasma penetrates into the axis-cylinder through Ranvier's nodes.

4. Lecithin, a body composed mainly of hydrocarbons and phosphorus, the active constituent of myelin and a prominent component of the electric organ of the ray, when exposed to the action of the oxidizing substance liberates energy: i.e., nervous energy.

Continuing our quotations from Professor Barker's article, we will introduce the various points of comparison which appear to us to sustain our interpretation of Apáthy's neuro-fibrils. "Inside the ganglion-cells a reticulum of fine fibrils derived from the neuro-fibrils in transit can be stained a beautiful deep-violet color by Apáthy's chloride-of-gold method." That the latter method can be considered as similar in action to the methylene-blue method and that the stain follows the same channels and affects the same chemical constituents of the plasma is shown by the following remark of Professor Barker's: "With a little care and a good sample of methylene-blue the *nerve-endings* and the *axis-cylinders* of medullated fibers, with which they are continuous, can be stained in a way far surpassing in constancy and completeness the best results of the uncertain gold-chloride procedure." As the methy-

lene-blue and a modified chloride-of-gold stains were those mainly used by Apáthy, no confusion can occur on this score.

Indeed, if we convert all of Apáthy's neuro-fibrils into minute capillaries, their identity as inherent parts of the general circulation is placed on a solid foundation by the following remark of Professor Barker's: "The doctrine of the fibrillary nature of the axon and unstainable portion of the protoplasm of the nerve-cell has recently received support from the studies of Lugaro[39] and Levi.[40] The former, too, in his studies of the nerve-cell under pathological conditions—for example, after poisoning with *lead* and *arsenic*—finds that the fibrils may become very distinct in the nerve-cells." That this directly points to the one system through which the morbid changes can occur, *i.e.*, the adrenal system, and that it precisely coincides with the foregoing remarks bearing upon this system, is evident.

The similarity of the neuro-fibril, on the one hand, to the axis-cylinder and its cell-body extensions, on the other, now becomes a normal consequence. "Each neuro-fibril is," Apáthy states, "made up of a large number—near its origin, at any rate —of 'elementary fibrils,' and in the course which it follows elementary fibrillæ are being given off at short intervals until finally the neuro-fibril itself may be reduced to a single elementary fibril." The fibrillary structure of an axis-cylinder is as clearly reproduced here as it can well be; the giving off of fibrils but typifies the irregular distribution of "non-medullated" nerve-fibers, and particularly those of the "sympathetic" system.

All this recalls a structure which appears to us to be intimately connected with the general circulation, the neuraxon and its cellular extensions, and Apáthy's neuro-fibrils—all being considered as component parts of the general vascular system: *i.e.*, Virchow's neuroglia.

The prevailing view concerning the rôle of this structure is that it affords a supporting frame-work for the nervous elements. Both in the white matter and gray matter the medullated nerve-fibers are separated one from the other by a network of glia-fibers. In the gray substance, however, the neu-

[39] Lugaro: Rivista di patol. nerv. e mentale, vol. i, 1896.
[40] Levi: Rivista di patol. nerv. e ment., vol. i, 1896.

roglia, though present in greater abundance, as a rule, than in the white substance, varies considerably, the net-work of fibers being especially thick in certain parts. "The neuroglia is present in greatest abundance in the gray matter immediately surrounding the central canal of the cord and the ventricles of the brain (the ependyma, as it is called)," says Stewart[41]: a suggestive feature in connection with the views submitted in the present chapter. The neuroglia-cells, as is well known, are of two kinds: those provided with mossy processes and those that have smooth extensions. A large number of investigators still consider that the latter represent true processes, and that, by freely anastomosing, they make up the mesh-work which surrounds the nerve-cells and their prolongations. Ranvier, however, after a searching study of the subject, was led to conclude that the smooth processes of these (stellate) glia-cells, were in reality neuroglia-fibers which merely passed through the latter in all directions, without forming part of the cellular structure *per se*. We have seen that Apáthy's neuro-fibrils, when they left the "nerve-cell," also passed *through* the cells after forming a reticulum in the latter: a feature which suggests that Apáthy's neuro-fibril and the neuroglia-fiber may be structurally similar.

It was formerly thought that neuroglia was a variety of connective tissue, but this view no longer prevails. Indeed, so distinct is the latter from neuroglia that the two structures can be differentiated from each other by the simplest tests; thus, Ranvier and Malassez found that connective tissue placed in cold water was not modified after several days' maceration, whereas neuroglia-fibers were completely destroyed after two or three days. On the other hand, connective tissue was completely destroyed by prolonged boiling in water, while neuroglia was hardly altered under similar conditions. The suggestive relationship between Apáthy's neuro-fibrils and glia-fibers offers some ground for the belief that glia-fibers are also nervous elements. This appears to be sustained by the fact that identical results ensue when nerve-fibers and connective tissue are submitted to the last of the two tests mentioned, the

[41] Stewart: Physiology, p. 671, 1900.

nerve-fiber being merely rendered opaque, while the connective tissue is destroyed. As the latter is gelatinous, its destruction is easily accounted for, but why should the nerve-fiber be rendered opaque? Evidently non-medullated fiber had been used in the test, for medullated fiber is always opaque, while the non-medullated is translucent. We are led to suspect, in view of our belief that the axis-cylinder of a nerve contains blood-plasma, that it is the latter which became opaque during the boiling process. This is an important feature, for it would mean that neuroglia-fibers also contain plasma.

The identity of neuroglia-fibers as plasma-channels becomes emphasized when the morbid effects of poisons upon them and upon their cells are studied. Berkley[42] found the cell-bodies of the *vascular* neuroglia "larger, the protoplasmic extensions" being "thick and knotty and the arms extending *toward neighboring vessels* more prominent than in the normal." This was noted in slides derived from animals submitted to experimental acute alcoholic poisoning. When we consider that alcohol primarily stimulates the adrenal system with great violence and that the neuroglia closely invests the blood-vessels, it seems permissible to surmise that the thickenings and knots are dilations due to the centrifugal pressure of the plasma derived from the capillaries. Especially does this seem probable when the fact that "capillaries, like the intermediary vessels, are tortuous and twisted" is added to the rest of the evidence. And these alterations, besides an "exceeding abundance of the polynuclear leucocytes in and around the cerebral vessels," etc., are not peculiar to alcohol, for Berkley emphasizes the fact—demonstrated for the first time—that the lesions produced "are very similar to the pathological lesions produced by other more virulent soluble poisons": additional proof that the adrenal system underlies the morbid process. Serum-poisoning was also found to cause great swelling of the bodies of the vascular neuroglia, "thick groups of these swollen cells" surrounding "nearly all the vessels of any size in the gray layers." In ricin poisoning Berkley found the cell-bodies "universally much larger than the control," and "apparently

[42] Berkley: Johns Hopkins Hospital Reports, vol. vi, No. 1.

swollen, even globular in outline." The extensions were also thicker and more nodular. "Are these elements, which belong to the *lymphatic* apparatus," queries the author, "taking up *detritus* from the degenerating protoplasm of the nerve-cells and becoming engorged?" The conclusion that they belonged to the lymphatic system was reached because they were found to contain *lymph*, which, in the language of Johannes Müller, is "blood without its red corpuscles": *i.e.*, *blood-plasma*, and, of course, its due proportion of oxidizing substance.

Evidently then, it is the *plasma* found in the capillaries of cellular elements of all organs which, crowded by excessive back-pressure (due to the marked contraction of the central vascular trunks induced by the poisons), causes the endothelial plates or cells constituting the walls of what Berkley terms the "intermediary vessels" to look, using his words, "as if they had been subjected to *severe strain*," as their even walls have "many irregular *bulges* in their outlines." That the neuroglia-fibers are the channels through which it is transmitted is also suggested by a remark made in connection with the effects on the gemmules, the retention of which, writes Berkley, "clearly shows that the swelling comes *from within* the substance of the stem and pushes the gemmulæ, which are still adherent, *outwardly* and apart."

Does a direct connection between the neuroglia-fibers and the protoplasmic processes of neurons exist, as suggested by the fact that Apáthy's neuro-fibrils are stated by him to penetrate the cell-bodies—provided his fibrils *are* glia-fibers? To establish this upon a firm basis, the thickening, bulging, etc., found by Berkley upon the vascular neuroglia must also be shown to extend to the processes of the neuron.

Golgi has expressed the opinion that the greater part of the nerve-cell—*i.e.*, the entire structure excepting the axis-cylinder—was concerned with its nutrition: a view which met with considerable dissension. Among the opponents of this interpretation was Forel,[43] who contended that the entire cell was simultaneously endowed with nutritional and functional attributes. This conception was defended by Ramón y Cajal,

[43] Forel: Archiv für Psychiatrie und Nervenheilkunde, vol. 1887.

and seems likewise sustained by our analysis, so far. Indeed, we have seen that the axis-cylinder, if our interpretation is sound, is able, through the presence of its coat of myelin and its plasma-containing fibrils, not only to supply chemical—probably nervous—energy, but also to undergo nutritional metabolism. Can we say the same of the cell-body of the neuron?

We have seen that the fibrils penetrate the nerve-cell, and that various poisons, as shown by Lugaro and Levi, cause them to become "very distinct." Referring to the intracellular distribution of the fibrils, Barker says of Apáthy: "He describes the finer peripheral neuro-fibrils as follows: They are seen to enter the cell-body and passing out to the peripheral part of its protoplasm, there to break up into a complicated plexus composed of anastomosing elementary fibrils in the outer chromatic zone. From this peripheral plexus there pass through the 'inner alveolar' zone radial branches to the internal chromatic zone, in which is to be seen another fine plexus of elementary fibrils, which, anastomosing and converging, finally form the single strong motor neuro-fibril, which passes out of the cell through the very center of its pyriform process. In other animals studied by Apáthy there are cells with definite dendrites entirely separate from the axon and in these the cellulipetal neuro-fibrils *enter by way of the dendrites*, ramify and anastomose freely inside the cell-body, and then, reuniting, *take their exit from the cell by way of the axon.* Similar relations exist in the ganglion-cells of the vertebrates which he has studied thus far."

This strikingly coincides with the course of the plasma-fibrils or capillaries as we interpret it. Indeed, if the fibrils enter the cell, form a plexus therein, and pass out "by the way of the axon": fibril, plexus, and axon represent a continuous channel which must contain plasma, since we have ascertained that the axon contains this fluid. Again we obtain a clear indication as regards the path of the blood-stream: it enters by the dendrites and passes out by way of the axon. It is with the dendrites, therefore, that the vascular neuroglia-fibers found thickened, globular, etc., by Berkley in his poisoned animals must be connected. But this fact suggests that these

structures should likewise present irregular swellings under the influence of the same agencies, and that the axis-cylinder should show less, the intracellular formation of plexuses and anastomoses interposing a barrier to the too free passage of plasma. That such is actually the case is illustrated by the annexed plates by Berkley, which represent the lesions found in the neurons of the poisoned animals to which reference has been made.

If the protoplasmic processes or dendrites are the first to bear the brunt of the vascular engorgement, the plasma being carried to them through fibrils connected with their tips, these tips or extremities should first show evidence of the expansile pressure. This is well illustrated in Fig. 1, a "*psychical* cell from the second cellular layer of the cortex," which shows, using Berkley's words, "a few pathological tumefactions on the uppermost branches of the apices of the apical dendrite. Otherwise the cell is normal." This cell was selected from a section derived from the brain of an animal poisoned with ricin, death having occurred in thirty-six hours. A feature of importance, however, is that it is the *main*, or apical, dendrite—that giving off the greatest number of subdivisions—which shows the evidences of engorgement; the extremities of the other dendrites are *not* thickened, but they show more or less marked evidences of engorgement as the main trunk is approached. This obviously suggests that the *plasma* penetrates the neuron by way of the main dendrite and that it finds its way into its collaterals cellulipetally; in other words, that, instead of also entering these collateral branches by way of their tips, it is supplied to them by the main trunk—precisely as if it were the main stalk of a plant. Of course, this does not mean that the apices of the collaterals may not subsequently show thickenings; being terminals, they should naturally do so when the pressure exceeds a given limit. This feature is illustrated by Fig. 2, especially by the larger stem of the main trunk. This cell, a projection-cell from the second layer of the cortex, shows the effects of forty-eight hours' ricin poisoning: *i.e.*, of somewhat more prolonged engorgement.

Worthy of special notice, also, is the fact emphasized by Berkley (referring to Fig. 2), that: "there is *now* distinct

diminution of the gemmulæ wherever the swellings are found" —which suggests that these minute ball-tipped projections from all collaterals are structurally similar to them, and that, when the engorgement exceeds in centrifugal pressure the resistance of a given area, the walls of the latter, including the gemmules, are more or less flattened out. Suggestive, likewise, is the fact that all the gemmules stand out boldly in both preparations. As many as thirty-six or forty-eight hours having elapsed before death ensued, the animals were evidently submitted to a primary period of intense stimulation, during which the gemmules were overdistended to such an extent as to cause them to lose their retractile property. Indeed, the sudden cessation of adrenal functions and consequent death must have left the cerebral structures much as if the animals had been suddenly killed.

Of marked interest in Fig. 3 is the presence at the extremity of the main, or apical, dendrite of a section of what appears to us to represent a fiber or capillary from which the neuron with which it is connected might have derived its blood-supply. The fact that it crosses its path suggests that the dendrite itself may be a branch of the vessel. Berkley describes this neuron as follows: "Projection-cell of the long apical process variety, showing numbers of large swellings of the protoplasm of the apical dendrite, thinning of the protoplasm of the stems in the interval between the nodules, and considerable loss of the gemmulæ along the margins. The lateral branches have mainly disappeared. The basal processes are retained intact."

The nodules seem to us to also illustrate the process through which the collateral fibers become detached from the main stem, as shown by the denuded cells represented by Figs. 4 and 5. The thinning of the plasma between the stems would account for the manner in which the lateral branches are detached, viz.: when the apical dendrite becomes sufficiently engorged the plasma ceases to circulate in one or more of the nodules, and the intervening protoplasm, failing to be nourished, disintegrates. That the basal processes should be the last to yield in this cell (corresponding in this with the condition of the same stems in Figs. 1 and 2) seems but normal

LESIONS IN THE NEURONS OF ANIMALS AFTER RICIN POISONING. *[Berkley.]*

[Johns Hopkins Hospital Reports.]

when we consider their proximity not only to the cell-body, which contains a large supply of fibrils, but also to the axis-cylinder (*ax.* in the drawings), which is the only centrifugal channel through which the engorged plasma can escape.

A feature of the cells shown by Figs. 1, 2, and 3 which strikingly links them to the adrenal phenomena brought on by toxics in the general organism is the fact that, although they are derived from animals in which the doses of ricin injected were reduced with each animal, the morbid phenomena as exemplified by each cell in turn are correspondingly intensified. In other words, the adult rabbit represented by Fig. 1 was given subcutaneously a dose of 0.5 milligramme, and death occurred in thirty-six hours: the cell only shows apical lesions. The second adult rabbit was given the half of the previous dose, *i.e.*, 0.250 milligramme, and death occurred in forty-eight hours: the entire apical dendrite and two of the collaterals are distinctly involved. The third adult rabbit was given the half of the last dose: *i.e.*, 0.125 milligramme, and death occurred in seventy-two hours: the apical dendrite is markedly studded with thickenings, and all but two of its collaterals have disappeared. It is, perhaps, unnecessary to lay stress upon the fact that this is due to the prolongation of the stage of adrenal stimulation: *i.e.*, of the time during which central vascular contraction caused peripheral capillary engorgement. And this need not be ascribed only to ricin. Berkley emphasizes this assertion when he says: "The poison *ricin*, whose action is in many ways *similar to that of many toxalbumins of bacterial source*, is capable of exerting a deep and extensive degenerative influence on the protoplasm of the nerve-cells of the brain." And this may further be extended to other toxics, for he also says: "Poisoning with alcohol in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum, very similar in character to the pathological lesions produced by other more virulent poisons." We thus have incontrovertible evidence that the unity of action displayed by all poisons, owing to the fact that the dynamic *source* of the phenomena witnessed is the one adrenal system, also extends to the nervous system. That the alterations in the elements

of the neuron should be due to the same centrifugal pressure that prevails in the capillaries of all peripheral structures during the stage of adrenal stimulation seems undeniable. Finally the fact that phenomena witnessed occur under the influence of poisons in general affords the complemental evidence in favor of our contention that *a neuron is directly connected with the circulation by one or more of its dendrites, which serve as channels for blood-plasma.*

Even the hæmorrhages brought on by adrenal overactivity, epistaxis, hæmatemesis, hæmaturia, etc., are exemplified in the engorged neuron shown in Figs. 6 and 7, and also from Berkley's series. The observation of Apáthy's, therefore, that his "cellulipetal neuro-fibrils enter by way of the dendrite, ramify and anastomose freely inside the cell-body, and, then reuniting, take their exit from the cell by way of the axon" finds its application *if, as interpreted by us, his neuro-fibrils are considered as blood-plasma channels.*

Still, the identity of the fibrils in the cell-body as blood-capillaries has so far only been suggested by the fact that they are continuous with the plasma-containing axis-cylinder and fibrils. While this constitutes strong evidence, the fact that they are blood-channels can only be determined by ascertaining the nature of the process in which the plasma takes part. This may probably be done by inquiring into the composition of a neuron's ground-substance.

The Physiological Chemistry of the Neuron.—What is the nature of the ground-substance: *i.e.*, that between the fibrils? After reviewing this subdivision of the general subject Barker says: "A neuron is made up, like all other cells, of nucleus and protoplasm. In the latter a centrosome and an attraction-sphere are present; at least it has been demonstrated in a certain number of nerve-cells. The protoplasmic portion of the cell can be roughly divided into a peripheral exoplasmic portion and a central endoplasmic portion. In neurons, as in muscle-cells, though less distinct in the former than in the latter, there is a tendency to a fibrillary structure, the fibrillæ tending to occur in the peripheral exoplasmic portion of both nerve- and muscle- cells rather than in the endoplasmic portion of the protoplasm. In both exo-

Fig. 6

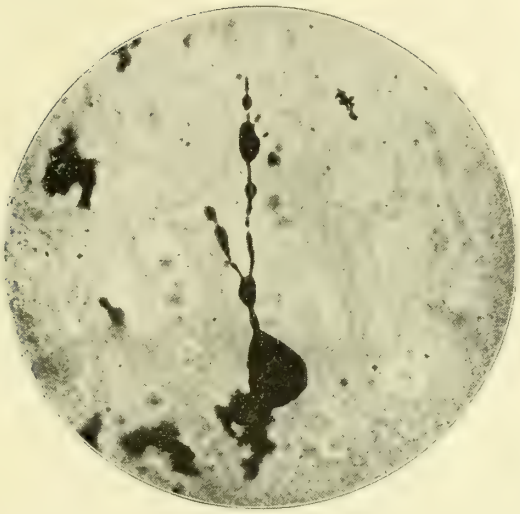
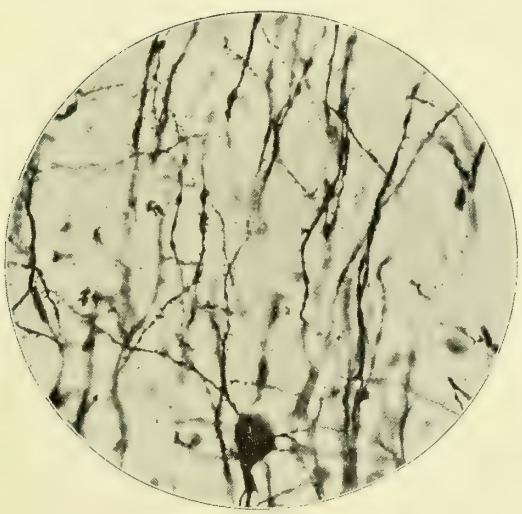


Fig. 7



LESIONS IN THE NEURONS OF ANIMALS AFTER RICIN POISONING. *[Berkley.]*

[*Johns Hopkins Hospital Reports.*]

plasm and endoplasm there can be made out in tissues which have been fixed *a more or less homogeneous ground-substance* in which are deposited larger and smaller masses of a granular nature. The ground-substance corresponds in tissues fixed with alcohol and stained by the methods of Nissl and Held to the 'unstainable substance' of Nissl, and the masses of granules to the 'stainable substance' of Nissl and the pigment.

"The 'stainable substance' of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells: a fact of extreme importance for nerve-anatomy and pathology. The axons appear to be entirely devoid of the 'stainable substance' of Nissl. Whether the stainable substances represent bodies precipitated from solution through the action of reagents or bodies pre-existent, though invisible, first brought into view through the action of fixing or staining reagents in the hardened tissues, in either case they appear to yield the chemical tests *characteristic of the group of nucleo-albumins.* Whether the staining reaction characteristic of the stainable substance depends upon chemical relations or upon purely physical conditions must, for the present, remain undecided.

"The 'unstainable portion' of the cell-body,—that is, the ground-substance,—though probably functionally much more important than the stainable, is not so well understood; its nature and structure are still as obscure as those of protoplasm in general." Still, the link with features previously brought out by our analysis now seems within reach.

Held has maintained that the stainable Nissl bodies represent simply substances precipitated from solution by the action of fixing mixtures; Fischer was led to the same conclusion. Barker says, in this connection, that he repeatedly convinced himself of the *homogeneous* appearance of the protoplasm of the nerve-cell when it is examined immediately after the removal from the living body. That the ground-substance is homogeneous, and that the unstainable portion is a product of dissociation of some of its constituents, are therefore probable. But the stainable portion we have seen has yielded the chemical

tests "characteristic of the group of nucleo-albumins." We are not, therefore, dealing with the group of nitrogenous fats to which lecithin, the main constituent of myelin, belongs, but with what probably represents, not a mere artifact, but an individual constituent which is precipitated by the fixing mixtures. It is important to determine, therefore, the exact nature of the Nissl "bodies," and perhaps by a process of exclusion ascertain that of the unstainable substance.

"Held," says Professor Barker, "undertook a most careful and exact chemical study of the granules in alcohol tissues. Thus, he found that the Nissl bodies are insoluble in dilute and concentrated mineral acids, in acetic acid, boiling alcohol, cold or boiling ether, and in chloroform. On the other hand, they are easily soluble in dilute and concentrated alkalies. With pepsin and hydrochloric-acid digestion he found that the ground-mass of the protoplasm vanished and that the Nissl bodies alone remained undigested: the reverse of what occurred on treatment with an alkali. The Nissl bodies yielded no reaction with Millon's or Adamkiewicz's reagent. Held obtained, however, slightly positive results with Lilienfeld and Monti's microchemical test for phosphorus, and a considerable quantity of the gray matter of the spinal marrow after digestion with pepsin and hydrochloric acid examined by Siegfried, of the physiological laboratory of Leipzig, showed the presence of phosphorus. Held concludes, however, from these various reactions, that the Nissl bodies belong to the group of the nucleo-albumins: a view which agrees with the investigations of Halliburton, who found in the gray matter a nucleo-albumin which coagulated at from 55° to 60° C. and which contained *as much as 0.5 per cent. of phosphorus.*"

The large proportion of phosphorus further sustains the preponderating rôle that the oxygen of the plasma must play in the neuron, owing to the activity of the reaction between these two elements. It also indicates a close relationship between the neuron and all other cellular structures of the organism. Thus, referring to Held, Barker says: "He asserts that in numerous experiments with his method (formol freezing) he has found in the *most different organs* constituents of the cell-body which behave not only tinctorially, but also mor-

phologically, *exactly* as the *stainable substance* in nerve-cells. He described them in *gland*-cells, *liver*-cells, in cells of the *pancreas*, in the cells of some sarcomatous tumors, in certain *connective-tissue cells*, but especially in normal and pathological *lymph-glands*. Cajal[44] also asserts that the stainable substance of Nissl is not specific for the nerve-cells, as he has demonstrated its presence in certain of the *leucocytes* and of the *connective-tissue elements*." Nissl's bodies appear to us, therefore, as constituting an organized component of the ground-substance of the neuron, a nucleo-albumin rich in phosphorus, which, judging from its similarity to a large number of cellular structures elsewhere in the organism, *represents the cell-structure itself*, precisely as is the hepatic cell when free from glycogen, bile, or the agencies from which these are derived. It is to the neuron what the neurilemma, Mauthner's sheath, etc., are to the internodal segment of a nerve, and includes — as does the protoplasmic membrane of Schwann—the nucleolated nucleus.

The unstainable portion must be the equivalent of myelin: the white substance of Schwann. We have seen that this is also unstainable. Even picrocarmine does not stain it, and Ranvier states that the axis-cylinder becomes stained at the nodes because there is no myelin in this region of the nerve. The similarity between myelin of the nerves and that of the cerebro-spinal system is emphasized by Foster when he says: "Obviously the fat of the white matter of the *central* nervous system and of spinal *nerves* (of which fat by far the greater part must exist in the medulla, and for nearly the whole of the medulla) is a very complex body indeed, especially so if the cholesterin exists in combination with the lecithin, or cerebrin (or protagon). Being so complex, it is naturally very unstable, and, indeed, in its stability resembles proteid matter." This also suggests, however, that protagon, a nitrogenous body containing phosphorus isolated by Liebreich from brain-substance, may be the unstainable substance we are seeking. Hoppe-Seyler and Diakonoff, having found it to be composed of lecithin and cerebrin, the direct connection with the former is not re-

[44] Cajal: Revista trimest. micrografica, vol. i, No. 1, March, 1896.

moved. Protagon readily breaks up into its constituents. Howell states that, "while protagon seems to be regarded as the principal form in which lecithin occurs in the brain, simple lecithin is believed to be present in the nerves and other organs," and he refers to Noll,[45] who found "the quantity of protagon in the spinal cord may amount to 25 per cent. of the dry solids; in the brain, to 22 per cent.; and in the sciatic nerve, to 7.5 per cent." That it is difficult to analyze this question is suggested by his closing remark: "Regarding the synthesis of lecithin in the body, or the physiological importance of the substance, nothing is known." We have seen the important rôle that it probably plays as myelin; its presence in such large quantities, as a constituent of protagon, in the cerebro-spinal system plainly points to it as of the unstainable ground-substance of the neuron.

What is the rôle of cerebrin, which, with lecithin, forms protagon, and from which it is readily separated? In a study of the chemistry of nerve-degeneration Halliburton and Mott[46] refer to the fact that they had previously shown that in general paralysis of the insane "the marked degeneration that occurs in the brain is accompanied by the passing of products of degeneration into the spinal fluid. Of these," say the authors, "nucleo-proteid and cholin are those which can be most readily detected. Cholin can also be found in the blood." Having continued this work, they now find "that this is not peculiar to the disease just mentioned, but that in various other degenerative nervous diseases (combined sclerosis, disseminated sclerosis, alcoholic neuritis, beriberi) cholin can be also detected in the blood." The tests that they employed were mainly two: (1) "the obtaining of the characteristic octahedral crystals of the platinum double salt from the alcoholic extract of the blood"; (2) a physiological test—and a very interesting one, we may add, if the functions of the suprarenal system are included in the process, namely: "the lowering of blood-pressure," which the authors consider as "partly cardiac in origin and partly due to dilation of peripheral vessels," and

[45] Noll: Zeitschrift für physiol. Chemie, Bd. xxvii, S. 370, 1899.
[46] Halliburton and Mott: Journal of Physiology, Feb. 28, 1901.

"which a saline solution of the residue of the alcoholic extract produces." This fall "is abolished," they further state, "if the animal has been atropinized." We may incidentally remark that these few lines embody the pathogenesis of most neuroses attended with degeneration,—if our views are sound,—since we have here the phenomena incident upon arrest of function, auto-intoxication, and toxic suprarenal insufficiency. But directly bearing upon the subject in point is the evident identity of cholin as a product of degeneration. It "has its source in lecithin decomposition and putrefaction," says Howell. But it is likewise, as we have seen, a waste-product of normal nervous-tissue metabolism, being eliminated with the bile in a modified form. That *cerebrin is also a product of putrefaction and of physiological metabolism* is suggested by two facts: it is found in pus-corpuscles and its formula and that of cholin present considerable analogy. Even taking as standard that furnished by H. Müller, which has given rise to considerable controversy, cerebrin is $C_{17}H_{33}NO_3$, while cholin is $C_5H_{15}NO_2$. *Lecithin, therefore, becomes the functional ground-substance of the cell-body of the neuron, just as it is in the nerve. Both in the neuron and its continuation, the nerve, therefore, the vascular fibrils carry blood-plasma, which, by passing through their walls, maintains a continuous reaction, of which the phosphorus of the lecithin and the oxygen of the blood-plasma are main reagents and chemical energy the end-result.* The relationship between the vascular fibrils and the ground-substance, nucleus, etc., is well shown in the annexed familiar engraving.

But lecithin, though a useful product of metabolism, requires in its formation the aid of protoplasmic function, as does, in the muscle, the elaboration of myosinogen. In the cell-body this is probably performed, we have seen, by structures which the Nissl bodies, as nucleo-albumins, represent. Indeed, in a study of the action of fixatives upon *protoplasm* Hardy found[47] that, "when a soluble colloid is fixed by the action of a fixing reagent, it acquires a comparatively coarse structure in the process, which differs wholly or in part from the structure of the soluble colloid." Again, that these protoplasmic

[47] Hardy: Journal of Physiology, May 11, 1899.

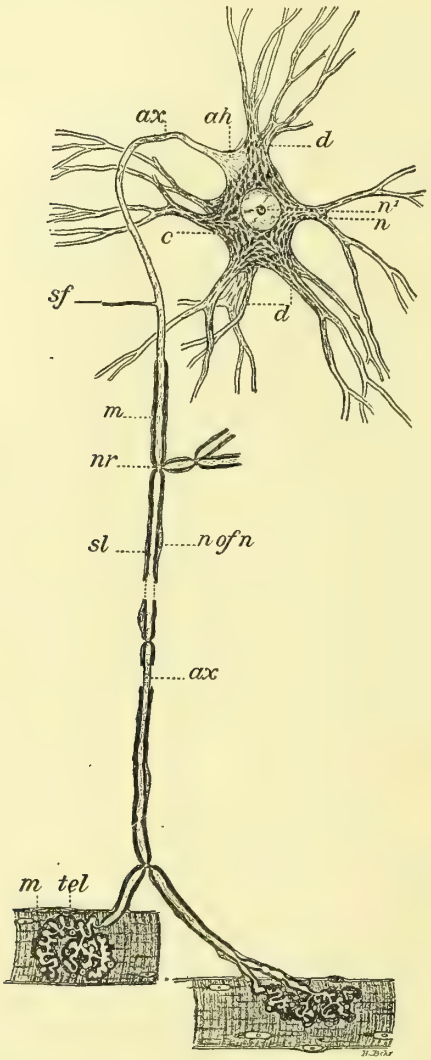


FIG. 3.—SCHEMATIC REPRESENTATION OF THE LOWER MOTOR NEURON.

The motor cell from the ventral horn of the spinal cord, together with all its protoplasmic processes and their divisions, its axis-cylinder process with its divisions, side-fibrils or collaterals, and end-ramifications (telodendrions, or motor end-plates) in the muscle represent parts of a single cell or *neuron*. *n'*, Nucleolus. *c*, Cytoplasm showing the dark-colored Nissl bodies and lighter ground-substance. *d*, Protoplasmic processes (dendrites) containing Nissl bodies. (*Barker.*)

structures are supplied by a vascular net-work similar to that of other cellular structures is shown by the observations of Apáthy, who took them for nerve-fibrils. Barker, referring to this feature of his investigations, says: "As to the relations of the neuro-fibrils to sensory surfaces, on the one hand, and muscular tissue, on the other, Apáthy makes very definite statements, especially in the last chapter of his article. A neuro-fibril entering the cytoplasm of an epithelial cell of a sensory surface in the leech breaks up (very much as in a ganglion-cell) into a *finer reticulum* composed of the *elementary fibrils*. A large number of the constituent fibrils, however, perhaps the majority, leave the cell in order to take part in the formation of a complicated *interepithelial fibril-plexus*." Neuron and nerve, therefore, appear to be similar to other organs as functional entities and to be subject to the same laws. Still, we can only state that analogy suggests that a neuron, its dendrites and nerve, in elaborating lecithin, *may* depend for their functional activity upon a nuclein rich in phosphorus found in the protoplasm of which their frame-work is formed and in the protoplasmic nuclei; for, as we will see later on, another source of lecithin exists.

The rôle of the blood-plasma is so clearly defined in the foregoing analysis that we deem it permissible to conclude that *all the component parts of a neuron—cell-body, dendrites, axon, and axis-cylinder—serve as channels for blood-plasma.*

Are dendrites provided, as are the cell-body and the axis-cylinder, with myelin? We have seen that, as stated by Barker, "the stainable substance of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells." He also states that "the axons appear to be entirely devoid of the stainable substance of Nissl"; but Berkley,[48] referring to the nerve-fiber terminals which are extensions of the axon, writes: "The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin *layer of myelin* nearly to their termination." As this refers to intra-

[48] Berkley: Johns Hopkins Hospital Reports, vol. vi, p. 89, 1897.

cerebral nerve-fibers, we are brought to realize that *the entire nervous system is built upon the same plan: i.e., of fibrils containing blood-plasma, surrounded by a layer of myelin. The main constituents of these bodies, the oxygen of the plasma and the phosphorus of the myelin, are thus brought into contact, and nervous energy is liberated.*

All this seems to us confirmed by the manner in which many, now paradoxical, phenomena are accounted for:—

The production of nervous energy, not only by the neuron, but also by the neural myelin, confirms the "avalanche" theory of Pflüger, which, though at first combated by Marey, was sustained by the latter after a series of experiments. Pflüger held that nervous excitation increased along the length of motor nerves: a view which strongly sustains our own. Duval emphasizes this fact, and states that, while the stream of impulses—which he terms "molecular vibrations," in perfect accord with modern physics—travels 28 to 30 meters per second, it "presents the characteristic of increasing gradually as it is transmitted, *i.e.*, as it advances in its nervous conductor." Richet has found that excitation of a sensory nerve was more intense when transmitted from the periphery than when excitation was applied to a part of the nerve nearer to its center (Duval). It is evident, therefore, that an accumulation of energy takes place in sensory as well as in motor nerves.

Our views are also sustained by the evidence afforded by nerve-degeneration. Quoting Turck's conception, Professor Barker refers to the Wallerian doctrine as follows: "Converting the Wallerian doctrine into terms of the neuron concept, the following law may be laid down: When it has suffered a solution of continuity, severing its connection with the cell-body and dendrites of the neuron to which it belongs, the axon, together with the myelin sheath covering it, undergoes in the part distal to the lesion acute and complete degeneration. This degeneration includes, not only the main axon, but also its terminals, together with the collaterals and their terminals connected with it." If the gradual increase of energy along the nerve, just referred to, is considered as a factor of the function and the sum-total of the energy utilized and is interpreted as made up of *neuron energy plus gradually increased nerve-energy,*

the following main facts connected with nerve-degeneration seem to us to find a ready explanation:—

Section of a motor nerve will cause degeneration of the peripheral fragment, and atrophy of the muscles supplied by it. We have emphasized the functional importance of a continuous supply of nervous energy, both upon the vascular and cellular elements of any organ.

There is no degeneration of the upper, or proximal, fragment, however, except as far as the first Ranvier node. This has been ascribed to traumatism, but we can readily understand now that section through an internodal segment destroys the mechanism of that segment, the supply of oxidizing substance failing to reach the myelin through the fibrils and their canaliculi. Its nutritional or "passive" function is thus arrested.

That the nerve and even its neuron require some of their own energy to permanently sustain their own life, as emphasized by Marinesco,[49] especially when long stretches of nerve are involved, is shown by the fact that if the seat of its ultimate distribution is destroyed,—a muscle, for instance,—or if it is disconnected from the latter, the nerve may, as sometimes occurs after amputations and peripheral neuritis, degenerate, and the process extend up to and include the cornual cell. That this does not always occur is doubtless due to the fact that the subdivisions of a nerve all contribute to the maintenance of its life, and that the chances that degeneration of a long nerve will occur are proportionate to the number of branches it supplies in its course.

The sensory nerves show the same attributes, but, of course, in a reversed direction. Section of the posterior root above a ganglion is followed by degeneration of the dorsal stump, which may include the extension into the cord. Amputation sometimes causes not only atrophy of the peripheral fibers, but also of the ganglion-cells and their prolongations in the columns. "The living muscle seems so organized that without nervous stimulation it can no more live than can the tropical animal without warmth or the rose without water,"

[49] Marinesco: Neurol. Centralbl., Bd. xi, 1892.

says Morel. How true this is is emphasized by the precaution Nature takes to nourish the nerve throughout its entire length and thus to insure the conversion of the chemical energy contained in its myelin and the plasma into nervous energy.

THE MINUTE CIRCULATION OF THE CEREBRO-SPINAL SUBSTANCE.—Such a circulation as that suggested by this title is not thought to exist. Both in the central ganglionic and in the cortical arterial systems the arteries are now believed to be "terminal": *i.e.*, to neither supply nor receive any anastomotic branch. They penetrate the cerebral substance to terminate there. The veins are similarly disposed. Deprived of valves and muscular tissue, they are likewise considered as "terminal" in the sense attributed to that word in respect to the arteries: a normal outcome of the absence of connection with the latter as supposedly indicated by the impediment presented to the injection of fluids in them. And yet, how does the blood, with its corpuscles, find its way from the arteries to the veins? Does it filtrate through the arterial walls, find its way through the lymph-spaces to the venous walls, and reach the sinuses? Of course, we have elsewhere in the organism both the effusion of plasma and the emigration of corpuscles through vascular walls; but this is a process of a different kind, and for which the blood-stream only plays the part of purveyor; it represents the main factor of a reparative and protective function, of which, indeed, the cerebro-spinal system is a prominent beneficiary when need be. There is a wide margin, however, between this process and the mechanism of circulation, which includes channels beginning at the heart and ending in this organ, and having for its purpose, not only to carry oxygen to all parts of the organism, but also to rapidly remove blood as fast as its oxygen-ratio is being reduced. "Terminal" vessels do not satisfy this *sine qua non* of perfect metabolism in the cerebro-spinal system, notwithstanding the presence in the superficial structures of more or less close capillary net-works. Indeed, the very presence of these capillaries seems to us to point to these deeper "terminals" as incongruities.

The marked evidences of engorgement so typically shown by Berkley's illustrations, and to which we have referred, are

characterized by a suggestive feature: *i.e.*, they occur, as far as the neuroglia is concerned, in the elements adjoining the blood-vessels or connected with them. Thus, Berkley writes: "In the silver slides the support elements proper, so far as the stain shows, present *no variations from the control*, but, on the other hand, the *vascular* neuroglia gives indication that alterations are taking place within its structures, and show considerable variations from control preparations. The cell-bodies are larger, the protoplasmic extensions are thick and knotty, and the arms extending *toward neighboring vessels* are more prominent than in the normal." As "the capillaries, like the intermediary vessels, are tortuous and twisted,"—evidences of intense engorgement, further emphasized by the "closely packed" white blood-corpuscles found in the vascular lumen, —it seems but logical that the engorged capillary and the engorged neuroglia-fibers should be continuous; otherwise the latter neuroglia swelling would remain unaccounted for.

Referring to the spinal cord, Berdal[50] states that "the moment the blood-vessels penetrate into the cord they become covered, on a level with the perimedullary neuroglia layer, with a coating of neuroglia, which follows them throughout *all* their ramifications and accompanies them along their *entire* course." Such a coating over cerebral capillaries would readily account for the engorgement of both structures to which we have just referred, since the channel, notwithstanding the alteration in its external aspect owing to the assumption of an extra coat, would, after all, be continuous. That such is the case is sustained by the fact that in what has been termed "chronic ependymitis"—doubtless a condition in which the layer of neuroglia becomes permanently engorged—a marked thickening of the tissue occurs (O. Israel). The increase of blood in the neuroglia-fibers which this morbid condition involves not only coincides with the swellings observed by Berkley after various forms of poisoning, but it is accounted for by the fact that ependymal neuroglia-cells were found by Marchi to send "a central extension which penetrates into the optic thalamus, where it subdivides to become *fixed upon the walls of the blood-*

[50] Berdal: *Loc. cit.*, p. 193.

vessels" (Berdal). This recalls the interesting feature in Fig. 3 of the plate opposite page 550. In the projection-cell represented the extremity of the long and irregularly-swollen apical process is also connected with the wall of what must be a diminutive blood-channel, if plasma is at all the cause of the cellular engorgement. Again, the neuroglia-cell, shown below, copied from an article by Andriezen, to which we will presently refer,[51] may be seen to be directly attached to a vessel. Indeed, we have Golgi's own testimony to the effect that some of the protoplasmic extensions of the nerve-cell are attached to neuroglia-fibers and to blood-vessels.

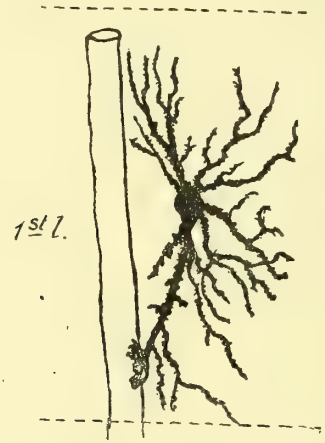


FIG. 1.—"A PROTOPLASMIC GLIA-CELL FROM A HUMAN BRAIN (FIRST LAYER OF CORTEX)." (*Andriezen.*)

The manner in which the neuroglia-cells and their fibers are connected with blood-vessels suggests that they are essentially different structurally, the neuroglia-elements being, not branches or subdivisions of the vascular system, but nervous structures which, at a given time during embryological development, became affixed to the vascular walls. This is sustained by the fact that neuroglia is, like all nervous elements, of epiblastic origin. Again, there is considerable analogy between nerve- and neuroglia- fibers. Foster emphasizes this fact when

[51] Andriezen: Brain, Winter, 1894.

he says: "Since the nerve-filaments, like the neuroglia-fibers, are very fine, and take, like them, an irregular course, it often becomes very difficult in a section to determine exactly which is neuroglia and which are nervous elements."

What is the rôle of the neuroglia and how is it functionally related to the true nervous elements? Suggestive, in this connection, are the following lines of Professor Foster's: "A medullated nerve-fiber of the white matter of the spinal cord resembles a medullated nerve-fiber of a nerve in being composed of an axis-cylinder and a medulla; but it possesses no primitive sheath or neurilemma. This is absent, and, indeed, is not wanted; *the tubular sheath of neuroglia* affords, in the spinal cord (and, as we shall see, in the *central nervous system generally*), the support which in nerves is afforded *by the neurilemma.*"[52] This conclusively shows that for a certain distance, at least, the neuroglia-sheath and the myelin act as coats for the one axis-cylinder: *i.e.*, for the fibrils containing blood-plasma. But we have seen that myelin is not the passive insulating substance that it is now thought to be; if our views are sound, it represents one of the two most important factors of nerve-composition, and, indeed, the main source of nervous energy. In modifying the accepted view concerning its functions, however, we have eliminated its rôle as insulating layer, leaving nothing but the neurilemma, or external, tubular investing sheath, for the protection and insulation of the "battery elements," as it were, the myelin and its oxidizing plasma. It is, therefore, this protective and insulating sheath that the neuroglia replaces in the white substance of the cord and in "the central nervous system generally": *i.e.*, wherever the myelin and its inclosed blood-plasma are present in the cerebro-spinal axis.

We have seen that, according to Barker, and as shown by the researches of Flechsig and Berkley, the dendrites of neurons are furnished with a thin layer of myelin nearly to their termination; while we have shown,—conclusively, we now believe—that their central canal contains blood-plasma. We have precisely, therefore, the structure of a nerve, minus its neu-

[52] All italics are our own.

rilemma. Indeed, the similarity even extends to the subdivision of the dendritic central canal into fibrils, for Berdal says, referring to the dendrites: "These prolongations seem striated longitudinally as is the cell, and appear to be composed of fascicles of fibrils which are continuous with those of the cellular body." A single structure is missing, however, that which, we have just seen, is represented by the neuroglia in cerebrospinal nervous elements: *i.e.*, the neurilemma. Obviously, the absence of a protective insulating sheath around the cell-body of the neuron and its extensions, considering their functional importance as generators of nervous energy, becomes absolutely incompatible with existing conditions, since the myelin would thus be exposed externally. Indeed, that the cell-body and its dendrites are supplied with an external sheath is shown by the following lines of Berkley's[53]: "Around the body of the cell we find an insulating mass of fluid contained in the pericellular lymph-sac, and as a capsule to the sac there appears a slight condensation of the tissue at this point that would take the place of a retaining membrane. This membrane apparently terminates where the first of the gemmulæ are thrown off from the ascending portion of the primordial process, and likewise at the location where the first buds appear on the basal dendrites. Does the insulating fluid and covering really end at this point? In absolute-alcohol sections of the cortex of the cerebellum taken parallel with the surface and stained with the anilines, particularly the blue-black, it is *quite readily demonstrable* that the thin membrane, which is now *undoubtedly composed of fine glia-filaments,* does not really cease at this point, but becomes attenuated, and continues to ascend *and cover the protoplasmic prolongations* of the cell." This speaks for itself; *the cell-body of the neuron and its dendrites are supplied with a covering which is to them what the neurilemma is to nerve-fibers; this covering is similar to that investing these nerve-fibers: i.e., a sheath of neuroglia.*

This only affords, however, information concerning the neuroglia supplied to the neuron *per se*, and to the structures which the axons become a short distance below the cell: *i.e.*,

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[53] Berkley: *Loc. cit.*, pages 90 and 91.

nerves. But we have still to study an important question: *i.e.*, the identity of the intermediary fibrils of neuroglia—important in the sense that it has a certain bearing upon the concordance between the older views of Gerlach and the modern observations and conclusions of Golgi. Indeed, if the entire cerebro-spinal axis is made up (as far as true nervous elements go) of these medullated glia-covered nerve-fibers and dendrites, we may well conclude with Gerlach that nerve-cells are united by an intricate net-work of extremely delicate nerve-fibrils. If, on the other hand, the cell-body, its dendrites, and its axon are alone medullated and glia- or neurilemma- covered, the connection *with the vascular system* being established by *non-medullated fibrils*, we are in accord with Golgi, who denies the existence of any connection through nervous structures between neurons.

That Golgi's view prevails is suggested—provided our own view that fibrils are plasma-channels is accepted—by the following lines by Professor Foster: "The larger part of the gray matter consists, besides a neuroglia supporting the nervous elements, of *nerve-filaments* running in various directions and forming, not a plexus properly so called, but an interlacement of extreme complexity." If the italicized words "nerve-filaments" are converted, in accordance with our view, into *neuroglia-fibrils*, the rest of the quotation will lead us to the solution of the question: "These filaments are, on the one hand, the fine *medullated* fibers spoken of above as being recognized with difficulty, and, on the other hand, *non-medullated* filaments ranging from fairly wide and conspicuous naked axis-cylinders down to fibrils of *extreme tenuity*, the latter arising apparently either from the division of axis-cylinders and nerve-fibers passing into or out of the gray matter or from the continued *branching of the nerve-cells.*"

The solution, it seems to us, lies in the fact that non-medullated fibrils exist at all, and that these range from fairly wide *axis-cylinders* down to fibrils of extreme tenuity, some of which, at least, appear to originate from dendrites. Indeed, this indicates that these non-medullated fibrils (of neuroglia, as stated by Berkley) represent the continuation of the main, or apical, dendrite (or dendrites, for there are often more than

one). Since these neuroglia-fibers are deprived of myelin, they cannot serve as sources of nervous energy, and merely represent, therefore, delicate channels through which blood-plasma, obtained by them directly or indirectly from a so-called "terminal" capillary, finds its way to the apical, or main, dendrite. The conclusion which this imposes seems to us self-evident: *A neuron is an autonomous organ as a source of nervous energy, and is supplied with blood-plasma through non-medullated neuroglia-fibrils, which are continuous with the external covering of its apical dendrites.*

Are Apáthy's fibrils, which, in the leech and earthworm, were found by him to penetrate the cell-bodies of neurons, the neuroglia-fibrils just studied? Gerlach, Haller, and others have also referred to the existence of delicate nervous net-works connected with the cells. The mere transformation of these fibrils into plasma-channels has enabled us, we have just seen, to link them with all the other elements of the function studied. In other words, we simply converted the fibrils into neuroglia blood-channels and found them to satisfy the requirements of the latter. Apáthy found that a neuro-fibril passed out of "a process of a nerve-cell": there is no fibril other than the neuroglia-fiber that is continuous with the apical dendrite that this neuro-fibril could represent. The neuro-fibril was found by Apáthy to be composed of "elementary fibrils": we have seen that this is precisely the arrangement within the neuroglia-fibers. He states that in their course "elementary fibrillæ are being given off at short intervals, until finally the neuro-fibril itself may be reduced to a single elementary fibril": we have quoted the statement of Professor Foster's that, as regards the "fibrils of extreme tenuity,"—those we found to act as neuroglia neurilemma,—they arose "apparently from the division of axis-cylinders." Finally, the neuro-fibrils, after freely anastomosing in the cell-body (having entered by way of the dendrite), are stated "to take their exit by way of the axon." This seems to us to conclusively show, in addition to the evidence adduced in the foregoing pages, that *Apáthy's neuro-fibrils and the various net-works thought to be composed of nerve-fibers by Gerlach, Golgi, B. Haller, and others represent the one and same system of neuroglia-fibrils, some of which contain*

myelin and blood-plasma and may, therefore, be considered as nerves, while others only contain plasma and are, therefore, blood-channels.

Under these circumstances, are the above-mentioned investigators not justified in considering the net-works referred to as nervous structures? They would be justified in doing so, did *all* the neuroglia-fibrils contain myelin; but it is the *absence* of this compound in the fibrils that serve as channels for plasma between blood-vessels and the apical dendrites of the neuron which seems to us to neutralize their view. Were there any evidence that a medullated fiber of any kind connects any portion of the cell with another structure capable of converting chemical energy into nervous energy, the question would remain an open one; but such is not the case; the absence of myelin in the neuroglia-fibrils connecting the neuron with the source of its blood-supply seems to distinctly point to the need of its absolute isolation, not only to avoid the promiscuous dispersion of the nervous energy it is able to produce, but also to enable it to store this energy and to direct it in the physiological paths.

The presence of the non-medullated fibers among the cerebro-spinal nervous elements becomes evident when the structural difference between the gray matter and the white matter is interpreted from the standpoint of our views. "Owing to the relative abundance of white refractive medulla," says Professor Foster, "the white matter possesses in fresh specimens a characteristic *opaque* white color; hence the name." . . . "In transverse sections of the cord *nearly the whole* of the white matter appears, under the microscope, to be composed of minute circles, the transverse sections of the longitudinally-disposed fibers." . . . "The *gray* matter, from the relative *scantiness of medulla*, has no such opaque-whiteness, is much more *translucent*, and, in fresh specimens, has a gray or rather *pinkish*-gray color, the reddish tint being due to the presence partly of pigment and partly of blood, for the *blood-vessels* are much more abundant in the gray matter than in the white." That in the cerebral cortex, for instance, these vessels should represent the starting-point of the neuroglia non-medullary fibrils needs hardly to be emphasized. They are now

termed "terminal," but their appearance as such is readily accounted for by the fact that here, as in the cord, they are said to be imbedded in neuroglia, whereas, in reality, the latter, composed, as it is, of a mass of diminutive fibrils, is directly *affixed* to the vessel, acting precisely as would a multitude of minute subdivisions of the vessel itself. Each fibril (in which the blood-stream is so slender that it only appears "pinkish" through its translucent covering) is, in fact, a composite counterpart of the ependymal fibril and other neuroglia structures to which we have referred. In other words, *each neuroglia-fibril is affixed to the wall of the vessel either directly or through the intermediary of a neuroglia-cell, and therefrom extends to the main, or apical, dendrite, or dendrites, of some neuron.* In addition, however, this enables us to conclude that *a neuron receives its nutrition and its oxidizing substance directly from the general circulation,* and that *the blood which enters by way of the apical dendrites is distributed to the free dendrites and to the cell-body.*

A question suggests itself in this connection, however, viz.: How does the blood in the collaterals return to the main dendrite to find its way with the latter's blood into the cell-body? This appears to us to find its explanation in the following (already quoted) sentence, in which Berkley describes the cell-body: "Around the body of the cell we find an insulating mass of *fluid* contained in the *pericellular lymph-sac,* and as a capsule to the sac there appears a slight condensation of the tissue at this point, that would take the place of a *retaining membrane.*" The retaining membrane is doubtless the neuroglia covering of the collateral, as it is of the entire cell; underneath, therefore, is the lymph-sac—which *we* consider as a plasma-sac. But we have seen that Flechsig and Berkley's researches have shown that these "fine branches are furnished with a thin layer of myelin nearly to their termination." That this myelin must, as elsewhere, be supported by the neuroglia covering and in contact with it is evident: a feature which relegates the plasma toward the center, though in contact with the myelin. If we now recall the fact that fibrils have also been discerned even in these delicate collaterals, it becomes a question whether they serve to transmit plasma, centrifugally or centripetally. As

Berkley's experiments have shown that they become the seat of swellings under the influence of poisons, there must be no escape for fluids through their walls; indeed, gemmulation would become impossible were the centrifugal pressure necessary counteracted by the escape of the plasma into lymph-spaces. That the blood returns toward the cell-body and through some of the central fibrils is therefore probable. Under these circumstances we can say, as a working proposition, that *the plasma which enters the collaterals is returned to the apical dendrite, and to the cell-body with the blood of the latter. The blood of the cell-body then passes out through the axon.*

How does the blood leave the axon of the neuron in the substance of the brain and cord? This question plainly resolves itself into the following: How does the blood reach the veins from the axon? "The perivascular lymphatics . . . are especially found in connection with the vessels of the brain" says Gray[54]; "these vessels are inclosed in a sheath which acts as a lymphatic channel, through which the lymph is carried to the subarachnoid and subdural spaces, from which it is returned to the general circulation." This familiar fact would be unexplainable after the views we have advanced concerning the circulation of arterial blood were the return of blood to the veins not the purpose of the lymphatic *sheaths*, for the same authority states that lymphatic *vessels* "have not at present [1901] been demonstrated in the dura mater or the substance of the brain." Again, when we consider that *perineural*, as well as *perivascular*, spaces exist, we are brought to realize that by linking the axon of a neuron to a venule, with a lymphatic space as intermediary, we have the elements of a mechanism which not only utilizes structures that are *known* to be present in the cerebro-spinal axis, but which also satisfy the needs of the function. Finally, if an axon is itself buried (up to the neck of its bulbous terminals) in a perineural sheath, which in turn communicates with a vein through stomata, as is the case in nerves, the blood of the axon is provided with a clear path to the general blood-stream.

That the blood of the neuron is eliminated as it is in other

[54] Gray: *Loc. cit.*

nervous structures—*via* the axon—is evident; but do lymph-spaces connected with *veins* actually receive this blood? Referring to the effects of acute alcoholic poisoning upon the veins, Berkley says: "Changes in the coats of these vessels are similar to those in the arterial system, but aggregations of dying polynuclear corpuscles are more frequent, and are by far the most striking feature both of their contents and surroundings. These aggregations, which may vary from three or four to a dozen or more, are located both *within* and *without* the lumen of the vessel (especially the smaller ones). Within the lumen are collections of white corpuscles filling the interior, and numbers are seen *penetrating the walls.* So vast are the collections in the *perivenous spaces* that the whole cavity is occasionally filled, and backward pressure from the plugs and compression of the vessel from the outside have attained such a height that in a number of instances the vessel's walls have ruptured and *red* corpuscles are intermingled with the white and fill the space completely." These features are well illustrated in the annexed photographs. The center of Fig. 8 shows "polynuclear leucocytes in the perivascular space of a small intermediary vessel compressing its walls," while Fig. 9 shows "leucocytes in the blood in a cross-section of a large vein." The fact that the leucocytes are found in the "perivenous spaces" and "within the lumen of the vessel," coupled with the observation that they are "seen *penetrating* the walls," so clearly point to the process involved that further evidence seems unnecessary. *The blood* (we have seen that even *red* corpuscles are present) *of the axon evidently finds its way into a lymph-space connected with a vein, thence to the general circulation.*

Still, there is a feature of the whole process which requires elucidation. Why should the *veins,* which, of course, communicate with channels through which the blood can be freely evacuated, become *engorged* under the influence of the adrenal stimulation induced by alcohol? Engorgement of the arteries, their capillaries, the neuroglia channels, and the dendrites is a normal consequence of adrenal stimulation; but, the veins being outlets, such is not the case with the venous engorgement. This anomaly is accounted for by the now generally admitted fact that the vessels of the cerebral substance *per se*

Fig. 8

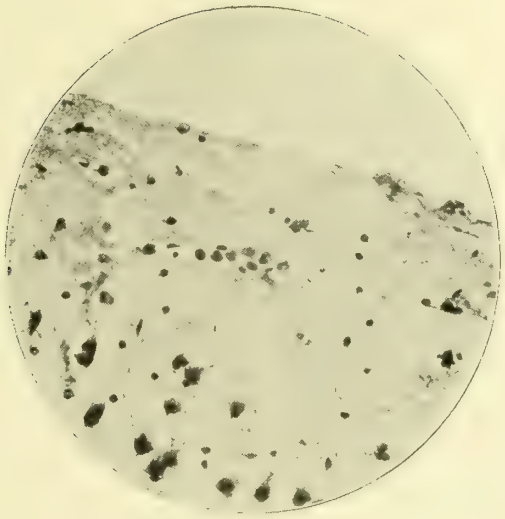
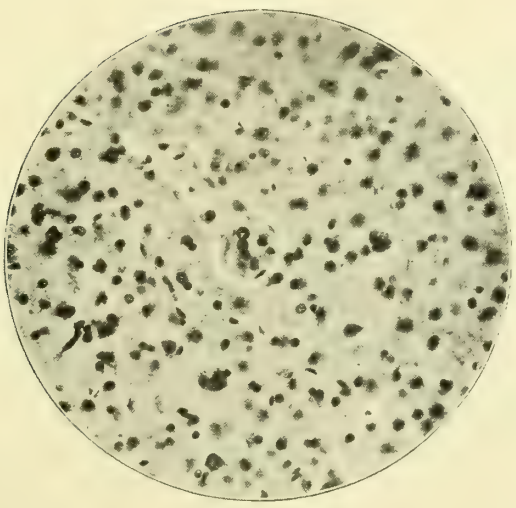


Fig. 9



LEUCOCYTES IN THE PERIVASCULAR SPACES AND IN VESSELS, AS A RESULT OF ACUTE ALCOHOLIC POISONING. *(Berkley.)*

[*Johns Hopkins Hospital Reports.*]

are not supplied with vasomotor nerves. "Vascular nerves may be found without trouble or difficulty in muscles, glands, etc., by the silver and other stains," writes Berkley, "but in the substance of the encephalon they are never to be seen with similar staining methods; hence it is fairly reasonable to suppose that they are not present in this location and that some other controlling mechanism takes their place. I have most carefully looked for them in many brains, both human and of the lower animals, but have never seen the slightest trace of their presence within the nervous structures. . . . Tuke and Andriezen, who made researches in the same field, have also failed to find them." As we will have occasion to show, this is an extremely important factor in the pathology of all toxæmias, mental and nervous diseases, for it indicates that *stimulation of the adrenal system by toxics of any kind causes vascular engorgement of the vascular channels of the brain-substance simultaneously with the engorgement of the peripheral capillaries of the other parts of the organism.*

Under these conditions contraction of the central vascular trunks through excessive adrenal activity causes not only congestion of the surface, but also of the brain. Strikingly confirmatory of this fact are the following statements of Professor Foster's: "It is argued that, in the absence of vasomotor nerves of their own, the cerebral vessels are wholly, so to speak, in the hands of the general motor system; so that when the blood-pressure is high, owing to a large vasoconstriction in the abdominal viscera, more blood must necessarily pass to the brain, and when, again, the pressure falls, through the opening of the splanchnic flood-gates, less blood necessarily flows along the cerebral vessels." . . . "Again it has been observed that certain drugs have an effect on the volume of the brain quite incommensurate with their effect on the vasomotor system."

If our views are sound,—*i.e.*, if our interpretation of the data available is exact,—our conception of the neuron's inherent functions coincides with some of the main conclusions reached by Deiters, Gerlach, Golgi, Forel, and Cajal. In outlining the conclusions to which these investigators were led, however, we will only refer to those which are directly connected with our own inquiry.

Deiters (1855) affirmed the prevailing theory—undemonstrated at the time—that the nerve-cell was supplied with two kinds of processes, the protoplasmic and the nervous, the latter constituting the nerve-fiber. Gerlach confirmed the views of Deiters, and showed that the protoplasmic processes subdivided into a fine reticulum, which, he thought, anastomosed with that of other cells. Golgi then demonstrated that, besides the two kinds of processes described by Deiters, there were given off collateral processes which, with the nerve-process, or axis-cylinder, constituted the only truly nervous structures of the cell, the other processes and the cell-body being purely nutritional. The subdivisions of the protoplasmic processes or anastomoses were not, in his opinion, continuations of those of other nerve-cells, either by continuity or through nervous networks, though some of the protoplasmic extensions were connected with neuroglia-fibers and blood-vessels. Forel contended that the entire cell and its processes were simultaneously functional and nutritional. Ramón y Cajal concluded that net-works of nervous fibrils did not unite the collateral processes, and, these being absolutely free, there could be no continuity of nervous substance between them, contiguity of their extremities alone prevailing.

We need hardly emphasize the fact that Golgi's views are strikingly confirmed by our own; indeed, had this great histologist converted the neuroglia-fibrils connected with blood-vessels into blood-channels, our interpretations would have been similar, though reached from entirely different directions. And we must admit that we consider this striking similarity, apart from the single line of research to which we have devoted all these pages,—*i.e.*, the microscopical anatomy of the circulation of the nervous system and the manner in which nervous energy is produced,—as a strong indorsement of our own conceptions. While Forel is fully sustained by our analysis when he asserts that all the parts of the neuron are simultaneously functional and nutritional, Golgi is likewise in accord with us when he considers the collaterals and the axon as the truly nervous structures, the others being nutritional. We have seen that the dendrites connected with the neuroglia-fibrils are really blood-channels. True, they are covered with gemmules

and lined with myelin, a feature which shows that they serve for the formation of nervous energy; yet this energy is not utilized in these dendrites, but by the collaterals, in addition to that elaborated by their own myelin. Nor is the greater part of the blood which courses through the main dendrites used by them; it passes into the cell-body: a great center for the *production*, we have seen, of nervous energy, which energy is mainly utilized, not by the cell-body *per se*, but by the dendrites and the axon through which the whole neuron's blood is continuously passing.

Golgi's observation that some of the protoplasmic processes were connected with neuroglia-fibers and blood-vessels furnishes histological proof that our interpretation of the manner in which the neuron is connected with the circulation is based on solid premises. The prevailing ideas, however, as to the nature of *neuroglia* normally suggested that his views included a nervous net-work as intermediary between cells, neuroglia-cells being likewise considered as truly nervous structures. Hence the affirmation of Cajal that collaterals were totally independent of one another, especially if he gave neuroglia-fibers and cells the credit of only being what they are now generally thought to be: *i.e.*, a "peculiar ground-substance," in which the "blood-vessels, the nerve-cells, and nerve-fibers" are "imbedded." The neuron *is* autonomous functionally: *i.e.*, as a nervous organ, *each neuron is connected with the circulation by its own neuroglia blood-channels.* An illustration of the continuity of neuroglia-fibers with the cerebral circulation is afforded by Berkley's experiments with alcohol. "Besides the swellings in the course of the dendrons," says this author, "we must always be on the watch to exclude certain processes of the support neuroglia-cells that traverse long distances of the cortex and exhibit a *pearl-string* swelling in the course of the fiber."

Are nerve-cells contiguous, as thought by Cajal? Berkley states that the great Spanish investigator writes "that the ascending fibers of the cortex, which have a vertical or oblique course through the medullary layers, have their points of contact with the protoplasm of the dendritic structures in the *intervals* between the short transverse processes (gemmulæ)

around which the ascending fibers twine." In other words, the tips, or extremities, of the axon of one neuron, instead of being in contact with the tip of the gemmule, touch the intervals between gemmules. "Such a discharge of the nerve-forces from cell to cell taking place at hundreds of indefinite points," continues Berkley, "could not fail to produce stimuli that would be more often aberrant than direct, and, in all likelihood, such an arrangement would produce the utmost confusion of thought and motion, a veritable inco-ordination of the cerebral functions, which would reduce direct cerebration to a nullity." This point seems to us to be well taken, and the identical argument prevails as regards contiguity, for if, as we believe, myelin and the oxidizing substance are constantly in contact in the neuron,—*i.e.*, the cell-body, dendrites, and axon,—nervous energy is continuously being formed, and promiscuous contact with the dendrites of other cells would give rise to the untoward effects enumerated. In the light of our views, therefore, continuous contiguity between neurons through their dendrites or axons does not appear possible.

How do neurons transfer their nervous energy to other neurons? Berkley states that it is "more than probable that it is only at the free bulbous terminations of the nerve-filaments [axons] that we have naked protoplasm, and from this uncovered nervous substance the dynamic forces, generated in the corpora of the nerve-cells, are discharged, through contiguity, on to the protoplasmic substance of other cells. Thus, in contradistinction to the hypothesis of Cajal," continues the author, "we have only comparatively few points at which the nervous forces may discharge themselves from axons to the protoplasm of other cells, and these are seated at definite points on the terminal arborizations of the nerve-filaments, for otherwise what would be the necessity of a terminal apparatus were the nerve-conductors free to discharge their dynamic forces at any point at which they came in contact with the substance of a dendron?"

It seems to us that the feature to ascertain in this connection is the character of the functions of the gemmules. Why do these little projections of the dendritic walls become erect during the cerebral congestion induced by poisons? Are they

really intended to receive discharges of nervous energy from the bulbous tips of axons? They outnumber the axonal end-organs out of all proportion. Indeed, their multiplicity around all the stems excepting the axon hardly points to them as terminals endowed with such important functions as those attributed to them. Again, Berkley states that "the twigs of the dendrites and the fibers touch each other frequently and in a manner that appears to be perfectly indifferent for the different kinds of nervous substance, receptive and projective." Such promiscuousness plainly testifies, it seems to us, against the identity of the substances in contact being exposed surfaces capable of transmitting to each other a stream of nervous impulses.

In the light of our views, however, a function perfectly in keeping with the experiments of Goddard in puppies, of Demoor with morphine, of Berkley with alcohol, ricin, serum, etc., suggests itself. We have seen that during functional activity the gemmules project, while during inactivity they recede. If we now connect these facts with the presence in the gemmules of a thin layer of myelin immediately under their external or limiting covering, and concede that the latter and the myelin take part in the formation of each gemmule, it will become evident that during the erethic state the surface of myelin exposed to the action of the oxidizing substance of the plasma will be greatly increased and the proportion of nervous energy produced correspondingly augmented. Retraction of the gemmules, on the other hand, by emptying them of their plasma, will normally cause diminution of energy-production, the myelin of the main channel sufficing to sustain nutritional functions during sleep, for instance, when the gemmules are retracted. We have what seems to us a counterpart of these minute structures in the muscle-cell, the myosinogen of the latter being replaced by the myelin. We have also, in the processes outlined, an *active* and a *passive* functional stage in keeping with other organs. All this so thoroughly coincides with the various attributes which the gemmules have been shown by various investigators to possess, that we feel warranted in concluding that *the gemmules are peripheral extensions of the dendritic walls having for their purpose to increase, when erect, the area of myelin*

exposed to the action of the oxidizing substance of the plasma, and thus to render the dendrite functionally active: i.e., able to transmit or receive nervous impulses. When the gemmules are retracted or collapsed, therefore, functional activity is in abeyance, as during sleep, anæsthesia, etc.: i.e., they are unable to transmit or receive impulses.

This tends to show that none of the gemmules serve *per se* to transmit impulses, and that the dendritic tips must alone be endowed with this function. That such is the case seems to us suggested by Fig. 2 on the plate opposite page 550, which exemplifies the condition of a dendron before the engorgement induced by ricin has become far advanced: *i.e.*, at a time when the dendron's lumen has not as yet become completely blocked. The two central dendrites may be seen to terminate with bulbous tips, while the remaining gemmules immediately adjoining the latter are not apparently enlarged. This would point to the enlarged extremity as a dissimilar structure in respect to the gemmules, a terminal organ as it were. Again, the gemmules and terminal organ would have presented a certain degree of resemblance under the influence of the engorgement under the action of poisons, had they been similar; their appearance, on the contrary, suggests dissimilarity. Berkley states that, "so far as the end-apparatus of the collaterals from the psychical cells is concerned, the terminations of the intermediary cells, the fibers entering from the medullated masses, all have the same end-apparatus, which consists solely of a simple freely terminating *bulbous ending*, situated upon the *extremity* of the finest branches of the nerve-fibers." As he then refers to figures in one of his illustrations which represent axons supplied with bulbar extremities, we infer that it is to the dendritic terminals that he alludes, and not to those of the gemmules, as a broad application of his preceding paragraphs might suggest. If the bulbous terminals of the entire dendrite as well as the axon are referred to, the quoted lines afford additional evidence tending to show that the dendritic extremities alone transmit or receive impulses. Indeed, in the article in which chronic alcoholic poisoning is studied, Berkley remarks: "The process of tumefaction *always* appears to begin at or near the fine extremity of the dendron, be it the

extremity of the main apical process or one of its *collateral* branches, and not infrequently the *extreme termination* of the dendron, is seen to be somewhat swollen *when no other portion of the cell is involved.*"[55] He also states that "in his description of the mode of ending of the *collaterals* of the great pyramidal cells" Cajal "describes their finest branches as terminating freely by a *nodosity.*" All these facts seem to us to warrant the conclusion that *each of the collateral dendrites of a neuron and each axon, or subdivision of the latter, is supplied with a bulbous end-organ.*

How is an axonal end-organ of one neuron functionally related to that of a dendrite of another neuron? Berkley, alluding to the subdivisions of the axon, each of which is supplied with its bulbous end-organ, says: "These spherical apparatuses are closely adjusted against the bulbous tips of the gemmules, at times the approximation being so close that the impression is given of actual contact, though it should be remembered that the slightest overlapping will produce the same effect; and, on the whole, it is more probable that there is no actual contact, but that the *axonal discharges* of the stimuli overleap the infinitesimal distance between bulb and gemmule." For the reasons adduced, we do not think that the gemmules serve for the reception of impulses. These reasons also suggest that each axonal end-organ can only discharge its stream of impulses into the bulbous *terminal* of a neighboring dendrite, which bulbous terminal would, under these circumstances, present some analogy with the end-bulb of Krause, and, indeed, with several peripheral sensory organs. We have also submitted reasons that seem to us to offset the assertion that the end-organs actually touch. Indeed, that an "infinitesimal distance" between the efferent axonal end-organ and the afferent dendritic end-organ exists seems to be the only conclusion warranted by the histological picture, as described by Berkley. It seems to us, in other words, that *each of the bulbous end-organs of an axon, though apparently in contact with the end-organ of one of the dendrites of a neighboring neuron, may be separated from it by an infinitesimal distance.*

[55] All italics are our own.

The bearing of this arrangement, as an element of function, asserts itself when the stress we have laid upon the *vibratory* character of a nervous impulse is recalled. When studying the nature of the functional activity of muscles, we had occasion to say, referring to the governing action of motor nerves: "As the vibratory rhythm of the impulse and that of the muscle always correspond, any variation of rhythm by the brain-center correspondingly modifies the muscular contraction." If we now analyze what this vibratory rhythm means when the dendritic end-bulb and the axonal end-bulb are separated by an infinitesimal distance, but one answer appears to suggest itself: *i.e.*, that there can be no flow of impulses from one to the other. But we must not lose sight of the fact that the contradictory histological pictures described by Cajal and Berkley are those of *non-living* cellular elements, and that death may leave the two end-bulbs juxtaposed, as seen by Cajal, or separated by an "infinitesimal distance," as seen by Berkley. Thus, each histologist is right in his way as regards dead tissue. But what of living structures? Cajal and Berkley will again assist us in reaching a deduction in this connection, for *each* investigator furnishes one-half of the main physical *function* involved: *i.e., vibration, which means rapidly alternating juxtaposition and separation of the bulbous end-organs.*

The rapidity with which the gap between the two terminals is opened and closed—*i.e.*, the *rhythm*—regulates, we have seen, functional activity. But can we conclude from this that non-activity of an organ means cessation of vibration of the bulbous end-organs involved in the function? We have seen that the nutritional processes of all tissues are continuous, nervous energy being supplied to the cellular elements as long as life lasts. Forel, as stated, was led by his admirable investigations to the conclusion that "living muscle appears to be so organized that without nervous stimulation it can live as little as the tropical animal can without warmth or the rose without water." This applies to all living tissues: a feature of the problem which necessarily implicates the continuous *development* of nervous energy and, as a consequence, an unceasing vibration of the end-organs. It seems to us, therefore, that, *inasmuch as the nutritional processes of the organism require a continuous*

supply of nervous energy, all the systemic axonal and dendritic end-organs are in a state of constant vibration.

In our analysis of muscular contractility we made the following statements: "The impulse-wave simply sets the muscle-elements to a given vibratory rhythm, and they retain this whatever be the intensity of the exertion required. . . . This may aptly be compared to the manner in which a note on a violin is made loud or soft. The power with which the string is pressed upon with the moving bow modifies the intensity of the sound; but the note remains the same. This means that its pitch does not vary, and if, for example, the lower C is given, we will know that the sound-wave of that note represents two hundred and sixty-one vibrations per second. So may the *impulse-wave* transmitted by the brain through a 'motor' nerve be represented by a fixed number of vibrations. Retraction, the muscle being then most tense, is therefore characterized by the greatest number of vibrations." If this interpretation is sound, it is likewise applicable to the "to-and-fro" motions of the bulbous terminals which constitute vibration, the number of these motions within a given time representing a given intensity. Any modification of the number of these to-and-fro motions within a given time, therefore, correspondingly modifies the intensity of the resulting vibratory impulse-wave, *the* PASSIVE *state of function (that during which cell-nutrition alone occurs) being represented by the lowest number of vibrations, the* ACTIVE *stage (during which the function is in full sway) by the highest number of vibrations compatible with normal health.*

Still, in accordance with our views, this applies to the impulses transmitted by the posterior pituitary body, since this organ, directly and through its extension in the cord, governs the passive stage of function and incites the cellular elements, both through the terminal vasomotors and the net-works distributed to the cells themselves, to higher activity when the active stage becomes necessary. Can we say the same of the independent hemispheres? This carries us back to the circulation of the brain, for the question involves another: *i.e.*, whether the cerebro-spinal functions, active and passive, are carried out in a manner similar to that of all other organs.

We are now able to say that they are, for *the neuroglia-fibrils of the substance of the brain and cord represent their blood-supply, just as the cellular capillary net-work of any other organ represents its blood-supply.*

Indeed, we must not overlook the fact that, while the neuroglia-fibrils representing the capillary supply of the cerebro-spinal substance are not supplied with vasomotor nerves, the peripheral vessels connected with the organ are, thus furnishing it with what we have termed elsewhere an *extrinsic* supply. This extrinsic system would thus be represented by the pial vessels, which, as shown by Andriezen,[56] are supplied with vasomotor nerves. "We find," writes this investigator, "that it is possible to stain the vasomotor nerves with Golgi's method. Starting from the carotid and vertebral plexuses we can trace them no farther than the circle of Willis by anatomical dissection (using a lens). Do nerves accompany the cerebral arteries as they go off from the circle of Willis; and, if so, how far; and what is their ultimate distribution? Our observations on the kitten's brain show that bundles of nerve-fibers accompany the middle cerebral artery (the one specially chosen for our study) and its branches in the pia. These fibers run in tortuous and zigzag fashion, and in the finer pial branches they can be seen to form a very fine (non-anastomotic) plexus of fibrils lying between the outer and the muscular coats. From this *perimuscular* plexus terminal fibrils issue which, running a short distance along the muscular layer either longitudinally, transversely, or obliquely, end in small spherules: little ovoid bulb-like arrangements abutting against the muscular elements (cells). We have succeeded in tracing these terminals and their distribution to the finest pial cells, but no farther. The intracortical continuations of the pial vessels have constantly failed to give us the least evidence of this perimuscular plexus, which therefore—so far as our investigations go—we are compelled at present to imagine as *stopping with the pial branches,* and *not* continued along the intracortical vascular branches."[57] This evidence, added to the facts already outlined concerning the pericerebral vascular supply, seems to

[56] Andriezen: Brain, Winter, 1894.

[57] The word "not" is alone italicized by Dr. Andriezen.

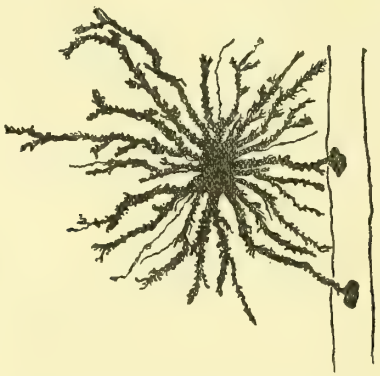
us to plainly indicate that *the cerebral circulation is governed, as is that of any other organ, by the posterior pituitary body, the vasomotor nerves of the pial vessels being terminals of the general motor system.*

This only furnishes us, however, the functional mechanism of the *passive* stage. In other words, the nervous energy developed owing to the presence of a given proportion of oxidizing substance (brought into contact with the myelin through the tonic vascular contraction insured by the general motor system) only causes the entire brain to create the nervous energy which, as we have seen, is essential to its own life. But how is the *active* stage incited in any one part of the cerebrum?

As is well known, groups of individual muscles may be caused to contract simultaneously, while some of the muscles which enter into the formation of these groups may be replaced by others. This is well exemplified by the mechanism of piano-playing: the index, thumb, and little finger, to form one chord; the annular and thumb to form the next, etc. Tracing this mechanism back to the structure which *incites* and *governs* the muscular adduction and abduction through which the keys are struck and released, we are brought back to a neuron. But how is the *neuron* incited to activity? In other words, how is the increased speed of blood through its myelin-lined dendrites, cell-body, and axon incited and governed? Can we ascribe this all-important function to the posterior pituitary body? We have seen that removal of the hemispheres did not prevent muscular action; a frog can swim, a pigeon fly, etc., and, indeed, continue to live a considerable time—months—if carefully fed, notwithstanding the absence of its hemispheres. This suggests that, while the posterior pituitary body either directly or indirectly incites and governs the functional activity of all organs, exception should be made of *the brain,* though it governs the circulation of this organ.

Still, the cellular elements of all organs are supplied with a net-work of terminal *nerves,* and it is through the intermediary in this net-work that its functional metabolism is governed by the posterior pituitary. How is the same function fulfilled in the hemispheres: *i.e.,* how are its cells, the neurons, "incited and governed"? Are they also supplied with

a net-work of fibrils which receives impulses from the posterior pituitary body? There is no evidence available to suggest that such is the case, and the functional relationship with the latter through the vasomotor supply of the pial vessels is the only link between the two organs that existing data permit us to accept. If, therefore, a regulative mechanism exists, it must be one connected with the vascular system, and so disposed as to enable it to govern the circulation through one or more neurons simultaneously. It must supply its own nervous energy, for we have seen that Andriezen found the vasomotor nerves to distinctly terminate upon the muscular coats of the



"A Protoplasmic Neuroglia-cell from the Human Brain (Fourth Layer of Cortex) Showing Two Expanded Conical Disk-like Attachments to a Vessel." (*Andriezen.*)

pial vessels; indeed, it must be as autonomous an organ as is the neuron itself.

Such an organ we have, it seems to us, in the neuroglia-cell shown in the above illustration, which Andriezen has named the "protoplasmic neuroglia-cell," and describes as follows[58]: "The protoplasmic glia-cell has a distinct cell-body, which is irregularly oval, frequently pyriform. Its various protoplasmic processes are of moderate length, they exhibit *great variations of caliber*, some being stout and coarse and others exceedingly fine. These processes are also *dendritic:* a thing never seen in the stellate cells. A most striking feature is the shaggy

[58] Andriezen: British Medical Journal, July, 1893.

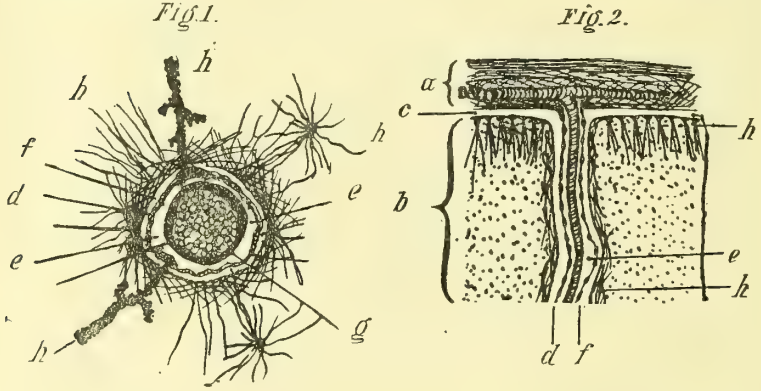
granular contour, as if a fine moss constituted the protoplasmic processes. . . . Further, by one or more of their *coarser* processes the protoplasmic cells are attached to the perivascular sheaths. The figure [on the opposite page] shows the cell with two such vascular processes, each *attached to the vessel* by a conical disk-like expansion ('foot')."

We could hardly produce stronger evidence than this in favor of our view that neuroglia-cells and fibrils are channels for blood. Bearing directly upon the question in point, however, is the fact that this cell, as indicated by its gemmules and its dendritic appearance, must be supplied with myelin. The association of this myelin with the blood-plasma in transit at this point—*i.e.*, so close to the blood-vessel—seems suggestive, for, if the illustration is closely examined, dendrites are not alone found around the cell, but also fibrils, which start from various parts of these dendrites. That these protoplasmic neuroglia-cells are directly connected with the blood-vessels so as to admit plasma is demonstrated by the fact that they also take part in the engorgement of neuroglia structures that follow poisoning. "The bodies of the *mossy* neuroglia-cells," writes Berkley, alluding to the effects of ricin poisoning, "are larger than normal, rounded, sometimes globular in outline, and the tentacles are thickened and knotty. There are general evidences that these structures of the *lymphatic* system are undergoing modifications of a pathological nature." We have already stated that this "lymph" was, according to our view, its next o' kin: *i.e., blood-plasma.*

Referring to the paper from which we have just quoted, Andriezen remarks[59]: "We also stated at the time that the evidence of staining with Golgi's method shows us a system of lymph-spaces surrounding the cell-body and its branches. Careful and fresh observation confirm us in this opinion, viz.: that there is *an exceedingly fine system of canaliculi and lymph-spaces* surrounding the body, and dendritic processes of the protoplasmic glia-cell, and directly continuous with the perivascular lymph-spaces." If the annexed sketches *by Andriezen* are now examined and *interpreted from our standpoint,* addi-

[59] Andriezen: Brain, Winter, 1894.

tional testimony in favor of our conception of the whole mechanism of brain-function will appear. Indeed, the *canaliculi* are evidently the openings into the neuroglia-fibrils. But these microscopical channels, which are often one-sixth the size of a blood-corpuscle, would soon be blocked were the latter allowed to reach them. There is interposed between them, therefore, a lymphatic membrane, similar to the one which, as we have seen, forms the lymph-space from which veins start. Here, however, a double purpose is served, as shown in the sketch. It forms two cavities: the one surrounds the blood-vessel, and



RELATIONSHIP OF THE VASCULAR AND LYMPH CHANNELS IN THE BRAIN. (*Andriezen.*)

a, Pia-arachnoid. *b*, Brain-substance. *c*, Epicerebral space. *d*, Adventitial sheath. *e*, Intra-adventitial space. *f*, Extra-adventitial space. (*According to our view, these are all blood-channels: The blood arrives in pial artery (g), and escapes through the walls of the latter into the "intra-adventitial" space (e). Part of the plasma of this blood passes through sheath d into the "extra-adventitial" space (f) and enters neuroglia-fibers and cells (h, h, h), and then passes into the apical dendrites of neurons; the rest of the plasma and all corpuscles return to the veins by way of the "intra-adventitial" space at e.—S.*)

represents the channel connected with the venous system, to which all corpuscles return; the other, or external, space receives only the blood-plasma which has passed through the membrane. The latter, being mainly composed of endothelial plates, is therefore phagocytic and bactericidal, and thus admits into the neuroglia canaliculi not only plasma relieved of all its

cellular elements, but also asepticized plasma. The outside of a vessel covered with a neuroglia-ridden sheath is shown in Fig. 3.

The two kinds of neuroglia-cells may be seen to take part in the formation of the external net-work of fibrils in the illustration on page 586. It is here, it seems to us, that the governing attribute of the "protoplasmic neuroglia-cell" shows itself, as suggested by the dendritic appearance of its exten-

Fig. 3

BLOOD-VESSEL OF THE HUMAN BRAIN, SHOWING SEVERAL NEUROGLIA FIBER-CELLS SURROUNDING IT AND FORMING A FELT-WORK (PERIVASCULAR SYSTEM). (*Andriezen.*)

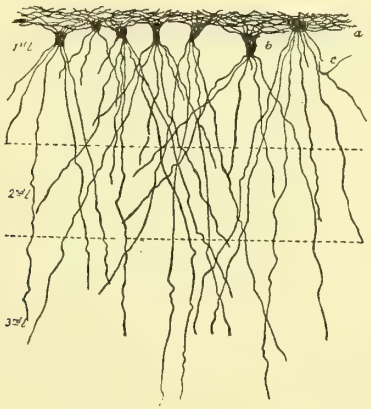
a, An encircling cell. *b*, Perpendicular neuroglia-fiber entering the sheath at right angles from a distant (extrinsic) cell.

sions. Indeed, Ranvier has been lead to conclude that the other variety of neuroglia (stellate) cell is not much more than a mass of aggregated fibrils in transit, the latter passing through them without forming part of the cellular structure. Still, as it contains a nucleus, it may possess a regulative action. The larger cell, however, imposes itself as an organ of a very active kind—capable probably of playing in the brain the part that the vagus plays in various organs: *i.e.*, to incite

active function and govern it in the neurons with which it is connected, either directly or through the intermediary of other neurons. The connection with the latter would be not established by continuous fibers, but through their end-bulbs, the axonal of the one to the dendritic of the other, etc., in order to allow of the transmission of *vibratory* impulses. Referring to these larger "protoplasmic" ganglia cells, Andriezen writes: "They occur abundantly throughout the gray matter, in all the layers of the cortex, but are rare in the white substance." Indeed, if our views are sound, the latter is a mass of axis-cylinders coming from the upper strata, and surrounded by their myelin, wherein energy increases with distance: a true "avalanche" — using Pfluger's expression — of nervous force toward the lower cerebral structures.

The predominating function of both varieties of neuroglia-cell asserts itself, however, when the characteristics of the cortical layers are reviewed. The first, or molecular, layer contains but few nerve-cells, according to Andriezen. Its proximity to the pial vessels normally suggests that, if glia-cells are intermediaries between these vessels and the brain-substance's circulation, they should occur in large quantities in this region. "Its outermost, or superficial, region is formed of a system of neuroglia fiber-cells," says Andriezen, and by means of the annexed illustration, among others, he emphasizes the varied directions and the length their extensions may assume. But if the illustration on page 586 is examined, the manner in which these cells (according to our interpretation) are supplied with plasma may be easily understood. As shown therein, the pial vessel dips into the brain-substance, surrounded by its lymphatic membrane in such a manner, we have seen, as to form two spaces, the internal of which is for the blood and corpuscles to be returned by the veins to the general circulation; the other, or external space, being that in which the plasma for the neuroglia-cells passes after penetrating the lymphatic membrane, in order to reach the neuroglia-fibrils. This affords a supply to both kinds of cells, which are seen to line the plasma-containing space. That both are intimately connected with the circulation appears to us beyond doubt; that the mossy, or protoplasmic, cell is endowed

with some function other than as a mere distributing center is as likely; that this function should be to regulate the circulation in the neurons, or groups of neurons with which it is connected (as shown by the effects of poisons upon all structures thus connected), is strongly suggested by the fact that, while the need of such a regulative system is evident, there is no discernible or known organ or system of organs, directly connected with the pial blood-vessels, other than these cells to which this important function could be ascribed. The following conclusions, therefore, seem to us warranted:—



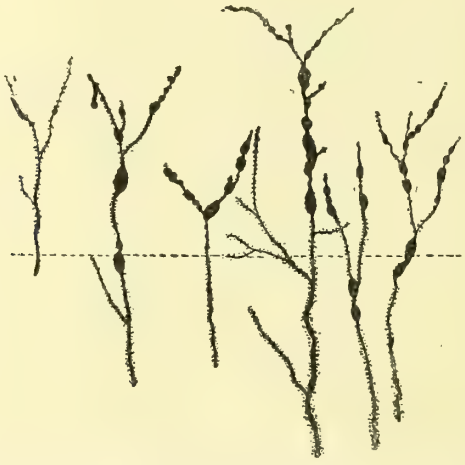
SEVEN CAUDATE NEUROGLIA FIBER-CELLS FROM THE HUMAN BRAIN-CORTEX (FIRST LAYER). (*Andriezen.*)

a, Tangential fiber-system. *b*, Cell-bodies. *c*, Descending fiber-system. The dotted line shows the limit between the first and second and the second and third layers.

The neuroglia-cells are the intermediaries between the general circulation and the capillary system (neuroglia-fibrils) of the brain-substance. The smooth stellate cell seems only to serve for the equable distribution of the blood-plasma to the neurons, while the mossy, or protoplasmic, cell presents the attributes of an organ to which the function of inciting a group of neurons to action by activating its blood-supply and of governing the quantity of nervous energy produced in these neurons can be ascribed.

Judging from the admirable histological work of Andriezen

and Berkley, the engorgement caused by poisons affects the three upper layers of the cortex most markedly. The bead-like swellings of the first-layer dendrites are well shown in the annexed illustration, the lesions being those found in alcoholic insanity. The second layer and third layer are represented by the plate opposite page 550, reproduced from Berkley's article, ricin poisoning, as previously stated, having been the cause of the cerebral engorgement. The cells of the last, or fourth (polymorphous), layer are not represented in the series



TERMINAL TUFTS AND ENDINGS OF THE PROTOPLASMIC APICAL PROCESSES IN THE FIRST LAYER (HUMAN BRAIN-CORTEX). (*Andriezen.*)

Showing bead-like and moniliform swellings, coalescence of fine miliary granules in place, and loss of fine granulation in the most affected parts. The dotted line marks the limit between the first and second layers. Alcoholic insanity.

of illustrations, but the fact that Marchi found that the ependymal neuroglia-cells sent a central extension to the optic thalamus, where it divided and became attached to the blood-vessels, represents but one of many examples which could be adduced to show that the circulatory system as we view it is that of the entire cerebro-spinal system, including the organ which governs the supply of blood to all tissues: *i.e.*, the posterior pituitary body.

THE POSTERIOR PITUITARY BODY AS THE CHIEF CENTER OF THE NERVOUS SYSTEM.

Howell,[60] in the course of experiments which led him to conclude that "the infundibular lobe of the hypophysis (the posterior pituitary) is, in all probability, not a rudimentary organ, but a structure that has some important physiological activity," found, as we have already stated, that "the extracts of the glandular lobe (the anterior pituitary) have little or no perceptible effect when injected alone. Extracts of the small infundibular lobe, on the contrary, have a distinct and remarkable effect upon the heart-rate and blood-pressure, an effect which resembles, in some respects, and differs, in others, from that shown by suprarenal extracts."

We have seen in our previous analysis of these observations that the symptoms produced were those of suprarenal overactivity. In other words, the extract acted like a toxic; the heart-beat was "not only slowed, but considerably augmented in force," says Howell, "as shown by tracings taken with a Hürthle manometer," etc. When both vagi were cut or a little atropine was given, the slowing of the heart was less marked. The result of vagal section is evident. As to the atropine, it prevented the slowing because it served to increase, when added to the pituitary extract, the dose of toxics in the blood, thus causing suprarenal insufficiency, instead of overactivity. But an interesting query imposes itself in this connection: The extract having, by its action upon the anterior pituitary, stimulated the activity of the adrenals, how did the former, through the increased oxidizing substance, bring about increased vagal action? The answer is easily reached: the posterior pituitary being also copiously supplied with blood, its activity is likewise increased. This emphasizes an important feature: *i.e.*, the fact that *the posterior pituitary is* functionally stimulated, as is any other organ, by the oxidizing substance in the blood passing through it. Indeed, the nerve-fibers which Berkley found to accompany the arteries suggest the presence of a functional arrangement similar to that of any organ, while

[60] Howell: "Transactions of Congress of American Physicians and Surgeons," vol. iv, p. 83, 1897.

the presence of so many neuroglia-cells at the apex—*i.e.*, where the posterior pituitary meets the infundibulum—indicates that the neurons which they supply are the seat of marked functional activity.

The salient feature brought to light by Howell's experiments, however, is the identity of the posterior lobe as only one containing an active agency. This obviously harmonizes with our views, since, as we have seen, the anterior lobe is, to a certain degree, passive in that it is stimulated to an inordinate degree only when toxics are present in the blood, while its normal activity is sustained by the secretion of the thyroid gland. Though the purpose of both organs is similar, therefore,—the conversion of chemical energy into nervous energy,—the manner in which this is done is not similar. Indeed, in the posterior lobe, the exciting agency is, as just stated, precisely as it is in any organ: *i.e.*, oxygen. The posterior pituitary must, therefore, become physiologically active through the same chemico-physical process that prevails elsewhere in the organism.

Indeed, we have seen that the posterior lobe is, in reality, but an aggregate of neurons—and a precious aggregate it must be, ensconced, as it is, in a bony cradle and resting on a pillow of blood, to preserve it against shocks or traumatisms! That, like all neurons, this aggregate depends mainly upon a phosphorus-containing ground-substance has been shown. We will recall, in this connection, the labors of de Cyon,[61] who, in the course of a large number of experiments, observed that: "1. Any, even slight, pressure upon the hypophysis (*i.e.*, both organs) immediately gives rise to a sudden variation of blood-pressure and to a notable reduction in the beats of the heart, the strength of which is at the same time considerably increased. 2. Electrical stimulation of the hypophysis, even with extremely weak currents, produces exactly the same phenomena as does mechanical pressure, but in a much more intense manner. 3. Extract of hypophysis, injected into the veins of an animal, produces upon the heart and upon blood-pressure effects that are analogous to those caused by electrical and

[61] De Cyon: Archives de Physiologie, July, 1898.

mechanical stimulation of this organ." To ascertain the identity of the agent which gave rise to these results de Cyon had the extract analyzed by as competent a chemist, M. Rossbach, as he is himself a physiologist, and ascertained that the active principle was *phosphorus*, evidently that of the only organ of the two which Howell found to be active: *i.e.*, the posterior pituitary body. It seems clear, therefore, that *the posterior pituitary body and the anterior pituitary body are both centers for the conversion of chemical energy into nervous energy, and that the posterior pituitary, being mainly composed of neurons and their protoplasmic extensions, is the seat of reactions similar to those that prevail in other neurons.*

The intrinsic processes upon which the physiological functions of neurons and nerves depend seem to us to be represented in the foregoing pages, but we have still to account for the "stormy processes in the nerve-fiber" to which Barker refers: *i.e.*, the exacerbations through which *passive* functions become *active*. Can we attribute these to the cells in the several centers? "Notwithstanding almost infinite minor variations in form," says Professor Barker, "the neurons in the most different parts of the nervous system present surprisingly similar general external morphological characteristics." We have seen, by the details furnished by the histological studies of Berkley, that such is not the case with the neurons in the posterior pituitary. Indeed, there are in this organ *ten* cells, exclusive of four of the neuroglia type that differ in morphological characteristics, each of which receives from Berkley a separate description. We have seen with what significant regularity all the axons of the cells in this lobe point upward: *i.e.*, toward the infundibulum. That a similar diversity of cellular shapes occurs in the latter is beautifully illustrated in the plate of Berkley's shown opposite page 594, and representing a diagrammatic drawing of a transverse vertical section of the infundibular region.

We have seen that above the infundibulum—*i.e.*, in the structures of the third ventricle—he found "varieties of ependymal neuroglia-cells, previously supposed to have entirely disappeared from the central nervous system," etc., and which were thought to be confined to "reptiles, amphibia, and fishes."

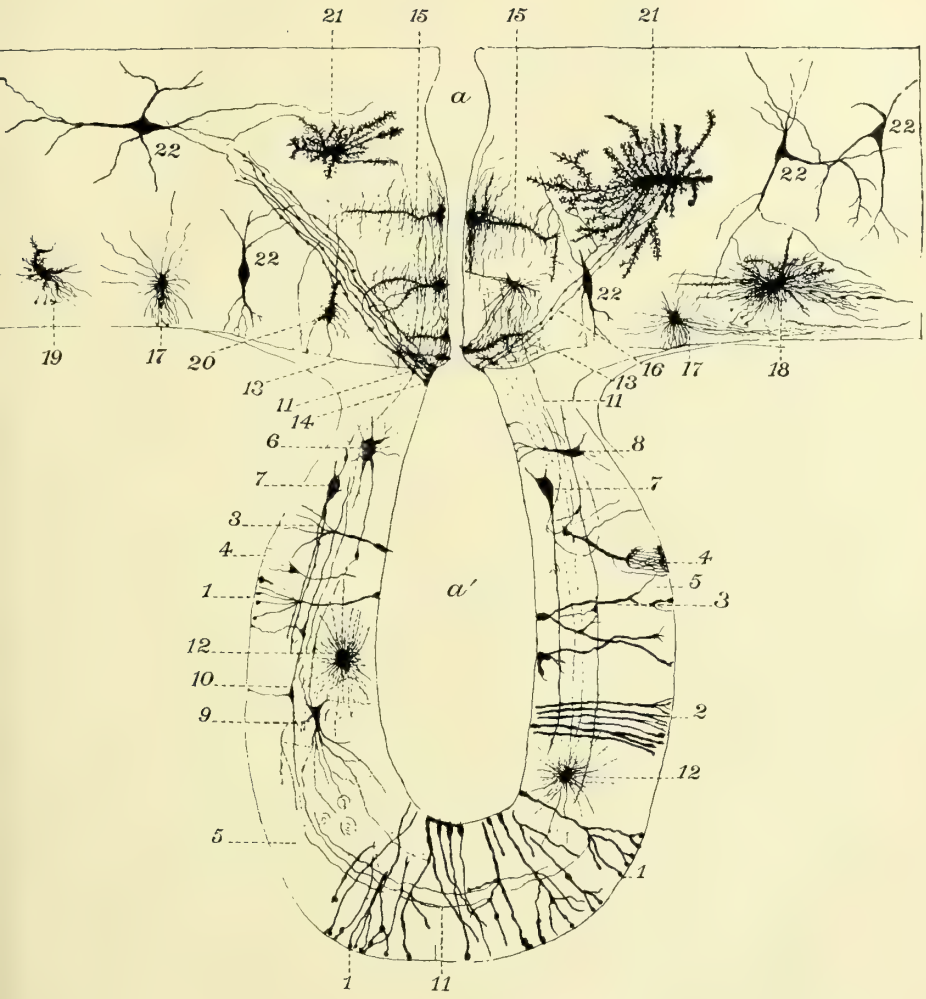
The physiological rôle we have ascribed to neuroglia-cells and fibers further emphasizes the importance of these structures and of the marked nutritional activity of which they are the seat. As a complement of this we showed that Andriezen traced a direct nervous connection in all classes of vertebrates between the "posterior lobe of the pituitary," on the one hand, and "the olfactory center" and the "bulbo-spinal centers," on the other.

When these facts and others reviewed are placed side by side with the adduced evidence (1) that the middle brain is the seat of a nervous mechanism through which highly differen-

TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION.

a, Lumen of ventricle. *a'*, Lumen of infundibulum. 1, Primary forms of ependymal neuroglia, the processes extending from a cell-like body at the edge of the ventricular cavity to the subpial limit. 2, Coarser and less ramified variety of ependymal cell. 3, Coarser ependymal cells, branching within the inner half of the infundibular wall. 4, Portions of ependymal cells with tufted subpial branchings. 5, Unstained nerve-cells. 6, Pyramidal cells with long, fine processes. 8, Transversely lying cells of small size with knobbed extremities. 9, Pyramidal cells with large numbers of apical processes. 10, Probable axis-cylinder extension of pyramidal cells with thickenings, and rectangular extensions to the subpial limit. 11, Nerve-fibers passing from the infundibular wall into the tissues along the border of the ventricle. 12, Burr-like cells of the infundibular wall. 13, Line of the floor of the brain. 14, Long-rayed ependymal cells of the juncture of the ventricular and infundibular cavities. 15, 15, Fir-tree ependymal cells of various sizes and forms lining the border of the ventricle. A few of them are seen to have rounded knobs adjusted against the pial limit of the basis cerebri. 16, Neuroglia cell approximating the short-rayed type of Golgi. 17, 17, Sustentacular glia-cells of the inferior border of the tuber cinereum. 18, 19, Glia-cells with numerous long and stout hairy processes from the bodies, and thicker projections, probably transition forms between the sustentacular cells and cells of later development. 20, Probable nerve-cell resembling some of the glia-cells. 21, 21, Large mossy cells situated at some distance from the ventricular border. 22, 22, Nerve-cells of different forms. (*Berkley.*)

tiated afferent impulses meet with response, and (2) that the structures to which Berkley and Andriezen refer are contained precisely in the central gray matter which Foster considers as "perhaps in point of origin the oldest part of the brain" and which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves," it seems clear to us that the posterior pituitary body is *a general center in which active functions are incited and governed in response to afferent impulses.* A neuron, we have seen, presents all the attributes of other organs; that the analogy includes the functional limits of these organs is very probable. Under these circumstances and taking



SEMIDIAGRAMMATIC TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION OF THE BRAIN. *[Berkley.]*

[*Brain.*]

the digestive system as example, a group of neurons constituting the origin of a nerve would be able to automatically continue its *passive* functions between meals. But just as the onset of digestion, the active functional state of the stomach, involves a reflex modification of the vibratory rhythm in all its nervous supply, through the vagus, *so would a nerve-center on passing from the passive to the active state reflexly receive from the posterior pituitary body the particular vibratory rhythm required by the organ to which its terminals are distributed.*

Professor Foster's reference to the central gray matter as a bed "for the development of the nuclei of the cranial nerves" suggests that the posterior pituitary might possibly supply energy for all cranial nerves. The complex origins and connections of the optic nerve would, under these conditions, convert the posterior pituitary into a source of energy, pure and simple, for general distribution.

But the variety of cells which the posterior lobe contains, as compared to the single type of ball-tipped fibers of the anterior, suggests that such is not the case. Berkley says, referring to the latter organ: "No nerve-*cells* are to be found in the substance of the organ, and all nerves belonging to it appear to be derived from branches of the carotid plexus." This indicates that nervous energy supplied by this organ to the suprarenal system, while produced through the action of oxygen upon the phosphorus-containing epithelial protoplasm and therefore similar in kind to that produced elsewhere in the organism, is due to a *stimulating* influence other than that which prevails in the posterior lobe. In other words, while the iodine in organic combination in the thyroid secretion is the *normal* stimulus of the whole anterior lobe,—and one of the many stimuli to which it responds,—the posterior lobe is made up of many types of neurons which depend upon the lecithin formed between their protoplasmic partitions for their functional activity.

The organs differ markedly and significantly in one respect, therefore: *i.e.*, in the fact that, while the whole of the anterior lobe is devoted to the one purpose of energizing the suprarenal nerves, the posterior is an aggregate of many centers. This indicates, it seems to us, that, if the organ were a

general source of energy for the whole bed of cranial nerves, irrespective of the individuality and purpose of each nerve, it would have been similar in general construction to its mate, the anterior lobe. That it is not distinctly suggests that *each group of neurons in the posterior pituitary body is a highly specialized center for a single class of nerves.* Indeed, this is experimentally, though indirectly, sustained by Andriezen's researches. He could not have traced a direct nervous connection with the olfactory bulb and with the cerebro-spinal axis had the organ been a center for the production of energy intended to be diffused promiscuously in the central gray matter.

Again, the connection between the posterior lobe and the nervous system cannot be limited to the cranial nerves, since we have seen how intimate is the functional relationship in which afferent impulses obtain, between the middle brain and the entire motor system. Were the cranial nerves alone involved, the skeletal muscles would have to be omitted from the list of structures under the organ's control. As we have seen, removal of the middle brain abolishes all "bodily movements," as Foster puts it, "carried out by means of co-ordinate motor impulses, influenced, arranged, and governed by coincident sensory or afferent impulses."

Yet, how can the posterior lobe influence organs with which it has no anatomical connection? Thus, the most prominent motor paths, the pyramidal tracts, arise, in the cortex, from the upper two-thirds of the central convolutions, pass down behind the knee of the internal capsule, and then penetrate the middle third of the pes cerebri, then the pons and the medulla, and finally pass down the cord. Where is the connection with the posterior pituitary? When the tracts "emerge from the pons," says Edinger,[62] "their fibers form two large bundles in the ventral portion of the medulla,"—*i.e.*, in the regions of the middle brain,—where, as we have seen, not only all nerves endowed entirely or in part with motor properties—the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, and twelfth pairs—are represented either by their nuclei

[62] Edinger: *Loc. cit.*

or by communicating roots, but also where *all nerves acquire their vasomotor properties.*

But what is the difference—as regards the rôle of the nervous energy involved—between a *motor* and a *vasomotor* nerve? None, evidently, and perfect equipoise between the energy transmitted to the cellular structures of an organ, and that necessary for its vasomotor functions, being a *sine qua non* to proper function, a single organ was intrusted by Nature with the *inciting* and *governing* rôle: *i.e.,* the posterior pituitary body. Of course, this relegates all motor impulses "influenced, arranged, and governed by coincident sensory or afferent impulses" to this organ, and makes it the general center of the motor system. We have previously referred to the fact that the medulla is only a transmitting center: a general station to which impulses from various directions arrive by the cord from below, by the commissures from the encephalic structures, and establish junctions with the several paths with which they are related. "The encephalon is a very complicated system of large and small continents of gray or central nervous substance," says Professor Duval, "communicating one with another and with the medulla by numerous commissures."

We have seen how absolutely independent of motor functions the hemispheres are, though volitional attributes enable them to *utilize* the motor system. Indeed, the experimental evidence adduced on this score is incontrovertible. But the same distinguished physiologist says: "The nerve-cells of the cord form in this organ a continuous central gray mass, extending from one extremity of the organ to the other. But, if the anatomist locates the superior limit of the cord on a level with the occipito-atloidian articulation, for the physiologist the cord extends into the interior of the cranium; it reaches to the aqueduct of Sylvius (the true origin of the motor oculi communis and patheticus) and even on a level with the third ventricle—the gray substance of the walls of this ventricle." We have seen that he also referred to its reaching up to the *sella turcica.* That it is *within* this bony structure that the main center of this vast mechanism—with its extensions and terminals, including the vasomotor fibers—lies we have sufficiently emphasized. We feel, therefore, that we have good

ground for the conclusion that *the posterior pituitary body is the center from which the impulses that incite and govern the functional activities of the general motor system originate.*

The relationship that exists between the cranial nerves and the posterior pituitary body now becomes apparent. Not only do the ten nerves endowed with motor properties either *in toto* or in part owe their functional impulses to this body, but those which regulate their functional blood-supply also. Again, as *all* organs require functional impulses and blood, and inasmuch as these impulses and the blood must be incited and governed, *all* organs must be functionally dominated by the posterior pituitary body. Indeed, all the data that we have presented in this work tend to show that *the posterior pituitary body is the chief motor center of the organism; it incites and governs the functional activity of all organs, including the vascular system and, through the latter, the brain.*

The anatomical relations of the posterior pituitary are shown in the annexed colored plate prepared by us to portray the relationship between this organ, the floor of the third ventricle, the medulla, the pons, and the cord—all of which structures are continuous.

THE POSTERIOR PITUITARY AS THE CENTRAL SENSORIUM.

From all the data submitted and the normal functional association embodied in reflex phenomena manifested through various nerves—the vagus, for example—motor-efferent phenomena are the normal sequences of sensory-afferent impressions, and the two are necessarily linked. The pons Varolii, or at least its *gray ganglionic substance,* is now thought to originate motor impulses that are independent of mental processes and to be the seat of *instinctive* acts. "It is, indeed, to the pons," says Professor Duval, "that, in a general way, we appear authorized to ascribe the most important rôle in great emotional expressions: laughing, weeping, the cry of pain; in a word, involuntary manifestations. It is in this sense that the term *sensorium commune* applied to the pons should be understood. Indeed, if, as was done by Vulpian, the *corpora striata,* the *optic thalami,* the *tubercula quadrigemina,* and the *cerebellum*[63] are

[63] The hemispheres had doubtless been previously removed.

THE POSTERIOR PITUITARY BODY AS GENERAL CENTER OF THE NERVOUS SYSTEM. *[Sajous].*

Showing Continuation from the Posterior Pituitary Body, of the Infundibulum, the Floor of the Third Ventricle, the Medulla Oblongata, and the Cord.

1, Corpora Quadrigemina. 2, Motor Oculi. 3, Patheticus. 4, Posterior Pituitary Body. 5, Supposed Vasomotor Area. 6, Cerebellum. 7, Abducens. 8, Trigeminus. 9, Fourth Ventricle. 10, Glosso-pharyngeus. 11, Facial. 12, Pneumogastric [Vagus]. 13, Auditory. 14, Hypoglossal. 15, Spinal Accessory. 16, Spinal Cord. 17, Superior Cervical Ganglion. 18, Left Hemisphere. 19, Third Ventricle. 20, Infundibulum. 21, Anterior Pituitary Body. 22, Optic Nerve. 23, Carotid Plexus. 24, Casserian Ganglion. 25, Spheno-palatine Ganglion. 26, Pons Varolii.

successively removed, the animal still shows, by characteristic agitations and *plaintive* cries, the pain it experiences when submitted to strong external excitations: *i.e.*, when its leg is squeezed with pincers or a bare nerve is excited. If the pons itself and the upper part of the medulla are now destroyed, the animal at once ceases to respond by similar cries and agitations." . . . "An animal that has lost its pons has therefore lost *a center for the perception of sensitive impressions.*" The gray ganglionic substance of the pons is, we have seen, a part of the central gray matter which begins in the posterior pituitary body: a fact which suggests that the latter is the seat of functions now ascribed to this part of the pons.

Indeed, these instinctive involuntary acts are dominant in the entire phylogenetic scale even in vertebrates devoid of skull or brain: the amphioxus, for example, down to which Andriezen traced the structures which ultimately become the pituitary bodies. It is difficult to conceive of an *inciting* and *governing* efferent impulse from the posterior pituitary without an afferent impulse conveying to it the needs of the organ to be incited to activity and governed. Duval refers to weeping, for instance; tears, we have seen, are brought on by increased circulation and stimulation of the cellular elements of the lacrymal glands; what is this but functional activity enhanced by impulses to the posterior pituitary—if our previous conclusions are at all warranted?

True, we are dealing primarily with a mental phenomenon, but this only proves that afferent impulses may reach the posterior pituitary from the cortex of the hemispheres as they can from any organ. Nor is the act an instinctive one; but this fact also affords supporting testimony, since it demonstrates that the organ is not only influenced by impressions of a purely reflex kind, or connected merely with organic life, but also by the highest form of nervous action: *i.e.*, mentality. What better evidence can we have of this than the violent cardiac action; the trembling; the involuntary excretion of urine, of fæces, of sweat; or even the sudden arrest of the heart, all of which phenomena may attend intense fear, and all due to loss of control *by the posterior pituitary*, under the violence of the mental impulses over . . . muscular tissue: cardiac, skele-

tal, cystic, intestinal, and sudorific? To this list me may add loss of control over all vasoconstrictors, since we have relaxation of the larger internal vascular trunks, central engorgement, in virtue of the principle—"vessels supplied with a muscular coat and capillaries are mutually antagonistic in contraction and dilation"—submitted in the earlier chapters and the mechanism of which we can now understand. Both antagonistic conditions are expressed in another symptom of fear: *i.e.*, intense pallor, the lividity of Asiatic cholera and, indeed, of the moribund. Truly instinctive, however, is the sudden cry or scream brought on by unexpected pain: evidently the result of an impulse to the posterior pituitary, since we again have a series of muscular actions of the chest, glottis, etc., which are necessary for the cry. Laughing, sneezing, coughing, and other kindred acts are all manifestations of motor activity; and so is vomiting the result of afferent and efferent vagal impulses, again with muscular structures as the mechanical factors and the posterior pituitary as inciting and governing organ.

And a striking proof of this is furnished by the fact that these manifestations of activity not only prevail in a frog deprived of its hemispheres, but that, if the animal is kept alive and in good health, signs suggestive of intelligence appear. "For days or even weeks after the operation," says Professor Foster, "there may be no signs whatever of the working of any volition; but, after the lapse of months, movements, previously absent, of such a character as to suggest that they ought to be called voluntary, may make their appearance. . . . Even in their most complete development such movements do not negate the view that the frog, in the absence of the cerebral hemispheres, is wanting in what we ordinarily call a 'will.'" Nor need they, for these so-called involuntary, instinctive acts are dominant even in vertebrates devoid of skull or brain: the amphioxus, for example, down to which Andriezen traced the structures which ultimately become the pituitary bodies.

That the posterior pituitary is a *discerning* organ, and one, at that, capable of simultaneously subserving many functions, is sustained on all sides. Totally independent of the brain, *though its servant when need be*, it appears to us as the undoubted seat of the many centers—*i.e.*, for cardiac action, respiration,

vasomotor action, sneezing, coughing, etc.—that have been located in the medulla oblongata. True, local disease or traumatism point to the "bulbar" areas concerned as "centers." But if the bulb is given the rôle which we believe it to fulfill,—one which, perhaps, may allow us to call it a *consociating* organ,—it will become apparent that any lesion capable of blocking the multitude of afferent and efferent impulses that traverse it at all times and which represent the aggregate of the organisms inciting and governing energy must necessarily compromise life or the functions of an organ to which the blocked nerves are distributed.

We have expressed the belief that there are but two general subdivisions of the nervous system, and that both of these have the posterior pituitary body as their general center. This view has not only been sustained by our analysis of the functions of the various organs, but it seems to us to fully coincide with established facts.

As Regards Efferent (Motor) Impulses.—It has been experimentally determined that all fibers that originate from roots in the *anterior* portion of the cord are *efferent: i.e.*, transmit motor impulses from the cord to the periphery. Section of these fibers causes: in muscles, paralysis; in glands, cessation of secretion; in vessels, dilation.

Interpreted from our standpoint, these morbid phenomena are accounted for as follows: As the *active* functional state of any organ is brought on by constriction of its arterioles beyond the limits of tonic constriction (that attending the *passive* functional state), section of the nerve transmitting the constrictive impulses brings on the opposite of active function,—*i.e.*, paralysis,—or, if distributed to a gland, arrest of secretion. Although the same impulses serve to *incite* and *govern* the cellular activity of the organ, paralysis, muscular or glandular, is not due to the loss of these two functional attributes, since section of vagal efferent nerves, which only incite and govern the active functional state beyond tonic contraction, does not cause paralysis. The immediate cause of the latter is slowing of the blood-stream: *i.e.*, reduction of the supply of oxidizing substance. The cellular elements lose their mechanical energy and can no longer be incited to action and governed. The

mechanical energy being due to the oxidizing substance, it is traceable through the adrenal system to the *anterior pituitary body,* while the inciting and governing influence, being of cerebro-spinal origin through the anterior root severed, is traceable to the *posterior pituitary body.* That it is of central origin is proven by the fact that section of the medulla is followed by general vasodilation.

Control experiments are represented by the well-known facts that stimulation of an anterior root causes vasoconstriction and increased functional activity, and, if sufficiently strong, convulsive movements of muscles. The latter, as we have repeatedly seen, are due to excessive oxidation of the muscular elements—complemental testimony to the effect that inadequate oxidation is the primary source of paralysis and that our conception of the functional process is not erroneous.

We have previously shown that the so-called vasomoter center and the cranial nerves that possessed motor properties occupied the same medullary region: the *upper.* As general motor nerves possess vasomotor properties, the reason for this is obvious. Again, we ascertained that the cranial nerves which acquire motor properties by anastomosis were grouped in the *lower* portion of the medulla. The entire organ thus becomes a conductor for general motor impulses, whether transmitted by the cord (as indicated by the general vasodilation incident upon medullary section) or by cranial nerves.

Although this aggregate of motor areas in the medulla represents but radiating paths from a common center, the posterior pituitary lobe, present conceptions as to their distribution—whether to the extremities, the thorax, the cranial nerves, etc.—or their anatomical relations with the hemispheres —the cerebellum, etc.—are in no way modified. All we need to recall is that—if our views are sound—the sympathetic system is not an autonomous system of nerves, and that it is a subdivision of the general motor system originating, like all motor nerves, from the cord, while its impulses emanate from the common general center. Indeed, *the bulb is a consociating organ, but not a primary center, nor the seat of a multitude of specific centers. It is purely an extension of the spinal cord; and its nuclei, roots, etc., correspond to the spinal roots, though more*

developed than the latter, and, like them, transmit impulses of which the primary functional source is the posterior pituitary body.

As Regards Afferent (Sensory) Impulses.—It has likewise been experimentally ascertained that all fibers that originate from roots in the posterior portion of the cord are *afferent: i.e.*, transmit sensory impulses from the periphery toward the cord. Section of these roots is followed by loss of sensation.

Interpreted from our standpoint, sensory impressions are similarly transmitted from all parts of the organism, and the one general sensory system supplies the needs of all. The nature of the impulse being governed by the specific cellular characteristics of the peripheral structures which receives the impressions, whether related to a special sense, general sensibility, variations of functional activity, etc., they all reach the posterior pituitary. That such is the case is demonstrated by the fact that, while frogs deprived of the hemispheres exhibit typical signs of continued co-ordination and sensation, removal of the bulb then causes them to no longer show these signs. This does not exclude the functions of subsidiary centers,—*i.e.*, reflex centers, ganglia, etc.,—which probably serve as accumulators of energy, and act in lieu of the posterior pituitary body unless the peripheral stimulation exceed their potential as to the efferent energy actively used. The law of generalization of Pflüger,—*i.e.*, propagation of (reflex) impulses to the medulla under excessive excitation,—which, according to our view, applies to the posterior pituitary, typifies the maximum effect produced under such conditions, and further demonstrates the connection between the periphery and the latter organ.

Control experiments are represented by the familiar results of stimulation of the dorsal roots, which causes augmentation of reflex activities and of conscious sensations. The reflex inhibition of functional activity of certain organs we have ascribed to excessive stimulation: in accord, therefore, with foregoing facts. This affords the complementary concordance required to place our conception of the functions involved on a solid foundation.

There is a feature of practical value in this connection

which must be emphasized: *i.e.*, the identity of the posterior pituitary body as the center upon which all emotions, shock, etc., react, and as the organ which initiates the phenomena that attend the impressions thus produced.

That this organ is directly or indirectly connected with the cerebrum in all phenomena pertaining to intelligence, reason, and will, precisely as its motor functions—other than the purely automatic ones—may be dominated by these higher manifestations of nervous activity, need hardly be emphasized. "Sensory" interpreted by us—*i.e.*, in its broad sense—refers to impressions received by all end-organs endowed with sensation, as previously stated. Whether these first reach the eye, the ear, the cutaneous surface, the gustatory papillæ, the olfactory area, etc., or be due to traumatism, surgical procedures, an abnormal mental state, such as attends fear, grief, or other emotions, etc., we are always dealing with molecular jarring of the posterior pituitary body: harmless when slight, pathogenic when sufficiently intense, but fatal when a certain limit is reached. Precisely as the current passed through the region by the Weber brothers inhibited the heart, so can fright, intense pleasure, or shock prove fatal by inhibiting the heart, but primarily by jarring the posterior pituitary body—or, speaking more correctly, by inducing excessive molecular vibration of its elements.

The maximum effect of shock thus becomes an arrest of nervous impulses through which function is sustained *via* the cerebro-spinal axis. This may well be illustrated by the description given by Professor Stewart of the "various phenomena which are grouped together under the name of shock" as exemplified by section of the cord. "When the spinal cord of a dog is divided,—*e.g.*, in the dorsal region,—all power—all vitality, one might almost say—seems to be forever gone from the portion of the body below the level of the section. The legs hang limp and useless. Pinching or tickling them calls forth no reflex movements. The vasomotor tone is destroyed, and the vessels gorged with blood. The urine accumulates, overfills the paralyzed bladder, and continually dribbles away from it. The sphincter of the anus has lost its tone, and the fæces escape involuntarily." We hardly need to emphasize the

fact that we have here a summary of all the phenomena which attend loss of functional activity: that over which the posterior pituitary body presides.

But this experimental section of the cord was also chosen as an example of the wonderful resources of Nature when life's functions are to be preserved. "If we were to continue our observations only for a short time, a few hours or days," continues the author, "we should be apt to appraise at a very low value the functions of that part of the cord which still remains in connection with the paralyzed extremities. But these symptoms are essentially temporary. They are the results of shock; they are not true 'deficiency' phenomena. And if we wait for a time, we shall find that this torpor of the lower dorsal and lumbar cord is far from giving a true picture of its normal state; that, cut off, as it is, from the influence of the brain, it is still endowed with marvelous powers. If we wait long enough, we shall see that, although voluntary motion never returns, reflex movements of the hind-limbs, complex and co-ordinated to a high degree, are readily induced. Vasomotor tone comes back. The functions of defecation and micturition are normally performed. Erection of the penis and ejaculation of the semen take place in a dog. A man with complete paralysis below the loins and destitute of all sensation in the paralyzed region has been known to become a father (Brachet). Pregnancy carried on to labor at full term has been observed in a bitch whose cord was completely divided above the lumbar enlargement."

How is this to be accounted for? Simply by the fact that the "sympathetic" chain of ganglia does not constitute an autonomous system, but a part of the general motor system, which is able to compensate, in a measure, even for spinal functions. It serves as conductor for impulses, through its communicating branches, and thus supplies a bridge, as it were, between the two segments of the cord: *i.e.*, between the isolated lower segment and its source of impulses, the posterior pituitary body. The same ganglia and the splanchnics also using this chain as intermediary to the adrenals, the continuation of the quasinormal functions in the mutilated animal are accounted for and the unity of the whole mechanism shown.

In view of all these facts, the following conclusion seems to us warranted: *The posterior pituitary body is the center upon which all emotions, shock—psychical or traumatic—and kindred sources of nervous functional excitement or depression react, and impairment of its functions accounts for the pathological phenomena now ascribed to such causes.*

THE PITUITARY BODIES AS THE GOVERNING CENTERS OF THE VITAL PROCESSES.

The foregoing facts sufficiently emphasize the physiological importance of the posterior pituitary body, for, in transferring to this organ the functional attributes so long thought to belong to the medulla and the pons in addition to others herein outlined, we have concentrated within its precincts *the entire control of all chemico-physical agencies that enter into and serve to sustain life's processes.* This, of course, indicates that even the anterior pituitary body is governed by its mate. That such is the case is evident: the terminal fibers that have been very properly termed "vasomotor" hold all vessels in their grasp, while it is through their intermediary that cellular metabolism and the oxygen-supply to *all* tissues are *incited* and *governed.* Indeed, this diminutive organ appears—to us at least—as one of Nature's most wonderful achievements. And yet, does the anterior pituitary not govern its mate? We have sufficiently emphasized the increased oxidation that occurs in *all* organs when this lobe is unduly active; that the posterior lobe is no exception to the rule is obvious. It thus becomes evident that both pituitaries are interdependent: a proof, indeed, of their supremacy over all other organic functions.

With due reserve, however, and fully realizing that all the deductions recorded in this volume may be faulty in the light of data with which we may not have been familiar, we venture to submit the following conclusion:—

The pituitary bodies are the general centers which actively sustain cellular metabolism: the anterior pituitary insures oxygenation of the blood and all oxidation processes; the posterior pituitary adjusts the vibratory rhythm of all nervous impulses which incite and govern functional activity.

This is not intended to imply that the pituitary bodies are

the source of life, for this is a property of every cell in the organism. During the earlier years of our existence, while the adrenal and nervous systems (including their chief centers) are undergoing development, their functions are relatively circumscribed, the thymus supplying deficiencies. As will be shown in the next chapter, we have evidence of this in the liability of children to certain infectious diseases which do not affect the adult. While the latter is able to counteract the pathogenic organisms and their toxins by means of adequate immunizing agencies, the child is not, because it is only supplied, through the intermediary of its thymus, with relatively inefficient quantities of these agencies; in other words, the total immunizing energy developed by its organs is inadequate. Indeed, the first year of a life is the period of greatest exposure: Nature supplies, in the mother's milk, not only nutriment, but, as previously stated, oxidizing substance—besides other antitoxic elements.

Even the anterior pituitary, the governing center of the oxidation processes, can in no way be deemed a life-center. During the earlier portion of its existence the organism is, in a measure, independent of its pituitaries, and able to sustain life with the centers of the lower brain and cord as governing ganglia. Even in the adult the adrenals are not solely dependent upon their own center. As we have seen, they are connected with the cord by communicating filaments: those which probably supplied them with their first impulses and sustained their functional activity until their chief center had reached a state of development able to satisfy the needs of the perfected organism. That these spinal communicating nerves may be able to resume or continue their rôle as channels for impulses to the adrenals, in case of injury to, or destruction of, the pituitaries, is probable. The very importance of these organs in the economy suggests the presence of a mechanism capable of insuring the continuation of life—even though incompetent to afford protection against disease.

The two pituitaries, intrusted, as they are, with functions which include high powers of differentiation, are complementary, and, so to say, terminal structures. They develop with the body, and are only functionally perfect when the latter has

reached its maturity; but the fact that they are *at all* subject to development proves their identity as parts of the whole, and though endowed with sovereignty over all functions, they stand no higher than any other organ as a life-center, though perhaps the seat of inordinate metabolism.

Oxygen, we have seen, is the active agency through which the anterior lobe carries on its functions; phosphorus is that upon which the posterior lobe depends—with the oxidizing substance of the plasma—for the elaboration of its intrinsic energy. These two elements underlie the functional activity of all cells, and their mutual affinity accounts for the display of vital energy of which all cellular structures are the seat. Oxygen-laden blood brought into contact with phosphorus-laden cells of which all tissues are built represents, therefore, the foundation of functional activity. Indeed, Pflüger,[64] referring to the photogenic organs of lightning-bugs, says: "Here, in the wonderful spectacle of animal phosphorescence, Nature has given us an example that shows where the taper burns that we call life. . . . It is certainly no rare exception, but only the special expression of the general law, that *all* cells are burning continually, although with our corporeal eyes we do not see the light."

[64] Pflüger: "General Physiology," by M. Verworn; translated by F. S. Lee, 1899.

CHAPTER XI.

THE INTERNAL SECRETIONS IN THEIR RELATION TO IMMUNITY.

THE UNITY OF CELLULAR LIFE.

In the present state of our knowledge the inaccuracy of the view that bacteria *per se* cause disease independently of the toxins they generate hardly needs to be emphasized. Apart from the mechanical effects which the accumulation of micro-organisms in the blood may cause, every disease distinctly traceable to them is attended with intoxication. Whether there occur after infection a rapid multiplication and a wide-spread distribution of germs, as in anthrax and septicæmia; or a more localized though prodigious multiplication of bacteria, as in cholera and pneumonia; or, again, an absolutely circumscribed multiplication at the site of infection, as in diphtheria: phenomena such as toxins alone can cause invariably appear. In the entire sphere of bacterial activity is encompassed that which is manifest in all Nature: a display of energy through change. Micro-organisms, by their growth and multiplication, not only generate products of metabolism, but these, by their physico-chemical effects upon surrounding liquids, engender the fermentative processes which underlie all infectious diseases,—"infectious" only in the sense of their being transmissible.

Again, we can legitimately assume that the reactions caused by micro-organisms in the body-fluids are similar to those brought on by the venom of snakes, insects, and toxic plants. Unity of cellular life applies to and includes all pathogenic cells, whether these be of animal or vegetable origin; it applies likewise to their metabolism, the toxic elements generated by them, and to the reactive effects on their surroundings. While Weir Mitchell, Reichert, and others have demonstrated the albuminoid nature of the toxic principles of snake-venom, Roux has emphasized the analogy between these principles and the toxalbumin of diphtheria. The urticaria

caused by the thistle is precisely that caused by the medusa, and is traceable to the same agency, formic acid: the irritating principle of the caterpillar, the ant, and other insects. Calmette[1] found that cobra-venom caused, in the conjunctiva, an inflammatory process precisely similar to that brought on by abrin and jequirity. We are also familiar with the beautiful experiments of Ehrlich with abrin and ricin: two albuminoid vegetable poisons which correspond with bacterial poisons even to their being able to confer immunity. Just as there are harmless cells in the animal structure, so are there harmless cells in vegetable structure. In the ascending steps of morbidity, in which these benign organisms may take part under the influence of various reactions, we witness, however, not only a biochemical parallelism in all phenomena engendered, but also, as rightly contended by Charrin,[2] a common symptomatology. Thus, in their physical interchanges, morbid effects, and semeiology, all cellular structures can be united in a common class.

THE ADRENAL SYSTEM IN ITS RELATIONS TO PHAGOCYTOSIS AND LEUCOCYTOSIS.

Metchnikoff terms "phagocyte" any cell deprived of a cellular membrane and capable of incorporating bacteria and other substances, and of disintegrating them. In the blood, certain leucocytes, particularly the mobile or wandering neutrophilic or polymorphonuclear forms (the "microphages"), the fixed endothelial and connective-tissue cells, those of the splenic pulp, and the large lymphocytes of the blood ("macrophages"), are endowed with this property. Precisely as do the familiar amœba, so do these phagocytes ingest bacteria and assimilate them. An animal is immune, according to Metchnikoff, as long as its phagocytes freely take up and destroy pathogenic organisms. In proportion, on the other hand, as the functions of the phagocytes are impeded, so is the animal susceptible to disease. That living and dead bacteria are thus disposed of seems to have been satisfactorily shown, while chemotaxis fairly accounts for the affinity which phagocytes

[1] Calmette: Annales de l'Institut Pasteur, vol., 1892.
[2] Charrin: "Poison des Tissus," quoted by Noé, *loc. cit.*

show for certain germs in preference to others. Metchnikoff's doctrine as regards the power of certain leucocytes, migrating and fixed, to act as phagocytes is sustained by experimental evidence; the process can easily be followed visually and the leucocytes be seen to ingest micro-organisms, to which they are drawn by chemotactic influence. In 1862 Haeckel witnessed the ingestion of indigo by leucocytes; in 1863 Recklinghausen observed that pus-cells were endowed with amœboid motion, and, having injected cinnabar grains in the dorsal lymph-sac of frogs, saw that they were ingulfed by cells floating in the lymph. Cohnheim in 1867 noted that the smaller vessels of the mesentery became dilated and saw leucocytes range themselves along the vascular walls, plunge their pseudopodia through the mural stomata, and penetrate beyond them, thus migrating and becoming "pus-cells." These pus-cells, in the light of Metchnikoff's theory, are the remains of protective microphages which have succumbed after migrating through vascular walls to meet offensively the pathogenic organism. Dead material, pigment-granules, fragments of tissue, dust-particles, indigo, ivory (in the osseous medullary canal, according to Kölliker), in fact, almost any foreign substance capable of invading the living organic structure, seems to become their prey. An aseptic catgut ligature, a fragment of bacilli-laden tissue, etc., soon becomes coated with an exudate filled with leucocytes which first ingulf the bacilli and then the disintegrated tissue. Let any inhibiting cause appear, however,—an excessively virulent germ, an abnormally high temperature, for instance,—their powers cease, and at once the bacilli multiply, causing death of the animal used for the experiment. The rapidity of the multiplication of pathogenic organisms is an additional factor operating against successful phagocytic action. When such is the case the phagocytes are themselves destroyed.

Successful phagocytes may be traced from their working field by staining the latter, as was done by Rosenberger; long lines of colored cells may then be seen to radiate in various directions from the stained area. The pathogenic germs, once ingulfed, usually cease to multiply, and, either through a toxic action or starvation, soon die and disappear. That organisms

are ingested alive Metchnikoff has shown. Spermatozoa, for instance, ingested by macrophages were seen to continue their motile activity until the tail had also been taken up. Begun in 1865 with the digestive epithelium of *Gedesmus bilineatus*, the cellular elements of which were shown to digest various extrinsic substances, Metchnikoff's labors developed in 1883 into his present doctrine of phagocytosis, which, notwithstanding much adverse criticism, is steadily gaining ground.

The rapidity with which the protective process is carried on in cases of general infection is well illustrated by Cantacuzene[3]: "Immediately after injecting anthrax bacteria in a vein of a rabbit's ear," says this author, "the organisms are taken up by phagocytes. At the end of seven minutes in the liver, eight minutes in the lungs, and one hour in the spleen none of the germs are free. Their destruction in the phagocytes is at first very rapid, but soon some of the latter are overcome, and the bacteria, by multiplying within them, cause them to become centers of pullulation. Still, the bacteria that escape from the dead phagocyte are seized by others; but, the number of the former becoming greater as the battle progresses, their protective powers are correspondingly reduced, and the bacteria finally invade the entire blood-stream. In the liver . . . practically all the bacteria are destroyed and digested within a few minutes after the injection. This superiority of the hepatic phagocytes in the fray lasts almost throughout the disease; but the activity of the phagocytes finally decreases; the bacteria multiply within them and become generalized. In the lungs there is rapid destruction of bacteria by polynuclear cells, then intracellular development of bacteria and generalization."

The phagocytes just referred to, the microphages, are wandering or migrating cells—free to respond and travel more or less promptly toward pathogenic bacteria, in virtue of the chemotactic attraction possessed by the latter.

Immediately connected with the rôle of these migrating cells is the process of leucocytosis,—a more or less transient or marked increase, in a given area or organ, of leucocytes,—the

[3] Cantacuzene: Quoted by Marcel Monnier, Gazette Médicale Belge, July 13, 1899.

polymorphonuclear variety, included among those which Metchnikoff termed microphages, usually predominating. Leucocytosis has been the source of considerable controversy. Some investigators have connected it directly with phagocytosis; others have ascribed to leucocytes the production of substances destined to endow the blood-plasma with antitoxic properties. That leucocytosis especially attends, besides leukæmia, infectious and inflammatory disorders, pneumonia, suppurative processes, rheumatism, etc., is well known. Inflammatory diseases of serous membranes,—peritonitis, pericarditis, meningitis, etc.,—malignant tumors, wasting diseases, hæmorrhages, etc., also show it at times. Various drugs produce leucocytosis, and it often follows cold baths, massage, and other stimulating measures. It is normally present in the newborn and often occurs during pregnancy, digestion, after violent exercise, etc.: the "physiological" form observed in normal subjects.

In contradistinction to leucocytosis is hypoleucocytosis: a condition in which the leucocytes are decreased. This is met with in typhoid fever, acute tuberculosis, lobar pneumonia, influenza, tubercular pleurisy, measles, inanition, etc. The causes of this condition may be said to be at least obscure, judging from the variety of doctrines vouchsafed by as many investigators and based upon contradictory experiments. Indeed, while some have observed leucocytosis in a given disease, other experimenters fully as reliable have witnessed hypoleucocytosis. While some have observed a primary decrease of leucocytes after the injection of toxic substances into the blood, others have noted that the capillaries of various organs, including the liver and the lungs, were crowded with leucocytes during this stage. That considerable uncertainty reigns as to the nature and purposes of leucocytosis is evident.

Leucocytosis, however, seems to present many bonds of association with phagocytosis, while the functions of the adrenal system as described in this work seem related to both. A rapid increase of leucocytes,—say, from 3000 to 10,000,—in typhoid fever, for instance, is thought to indicate that perforation is about to occur. And yet, Harvey Cushing[4] refers to

[4] Harvey Cushing: Archives Générales de Médecine, Jan., 1901.

four cases in which laparotomy was resorted to in this connection with the view of closing ulcers, in which none were found. While the operation led to no complications, it is obvious that leucocytosis, in this connection at least, proved misleading. This assertion is further strengthened by the fact that Cabot states that an increase to 15,000 leucocytes may be witnessed in the absence of complications. Colin K. Russel[5] analyzed the question in thirty-six uncomplicated cases and obtained a variation ranging between 2000 and 12,000. In one of the cases a leucocytosis of 28,000 led to operation; a perforation was found and the patient recovered. In another case the leucocytosis only reached 4800. Yet, operation led to the discovery of a ruptured bowel and six other ulcers which had nearly penetrated the whole thickness of the intestine. The patient died. A third case showed 14,500 leucocytes and was operated, but no perforation was found. While this in no way detracts from the great value of operative procedures in perforation, it seems evident that as a sign of this complication leucocytosis is unreliable.

Analysis of the cases in which laparotomy disclosed no perforation notwithstanding leucocytosis, however, may furnish a clue to the cause of these discrepancies and elucidate the physiological function involved. In one of the cases referred to by Russel (Dr. Hamilton's) the leucocytosis reached 16,000, but was 14,500 when the operation was begun. There was pain in the lower left quadrant and marked rigidity of the abdominal muscles. Nothing unusual was found beyond the condition of the bowel "to be expected at that stage of the disease." The next day the blood-counts revealed 10,000 leucocytes. The usual intestinal ulcers could alone, therefore, have been the source of the temporary exacerbation. In another case of the same kind, with a pre-operative leucocytosis of 17,000, the only feature found was unusual tension and swelling of the ileocæcal glands. As there was no perforation, we are relegated to the ulcerative process alone as the source of the symptoms witnessed. It is not with the perforation that this increase of leucocyte-count could be associated, therefore, but with the ulcerative inflammatory process.

[5] Colin K. Russel: Boston Med. and Surg. Jour., April 18, 1901.

Harvey Cushing refers to abdominal pain, rigidity and tenderness of the abdominal walls as having been observed by him in all cases some time before the perforation occurred. Are these symptoms due to the direct effect of the intestinal lesion upon neighboring structures, or are they localized expressions of a *general* perturbation? Lennander, of Upsala,[6] has recently shown that, while the parietal peritoneum—that immediately underlying the abdominal walls—was sensitive and painful even when only touched, rubbed, or stretched, the visceral peritoneum, on the contrary, could be rubbed, incised, cauterized, or chilled without causing the least discomfort. Neither here nor in the greater part of the small intestine, its mesentery, the great omentum, the cæcum and appendix, and the colon was there the least evidence of the presence of nerves capable of transmitting tactile, thermal, or painful impulses. If intestinal pain does appear, therefore, *before* perforation, the parietal peritoneum must be included in whatever protective process the threatened complication may awaken. The occurrence of this symptom elsewhere than in the neighborhood of the lesion further sustains this fact. E. Palier,[7] for example, describes a case in which abdominal symptoms were so marked that the diagnosis of appendicitis was made by a consultant and an operation performed. The autopsy showed pneumonia with empyema, the abdomen being normal. J. L. Morse[8] also refers to the danger of mistaking a case of so-called "abdominal pneumonia" in children for one involving the abdominal organs, and states that he has seen two cases in which the abdomen had been opened by experienced surgeons, because appendicitis was supposed to be present. Mirande[9] even goes so far as to suggest, in this connection, that a special form of pneumonia be distinguished: *i.e.*, that to which the name "appendicular pneumonia" has been given, owing to the predominance of the symptoms simulating appendicitis. These symptoms only occur, he found, in the early stages of the disease, and rarely persist longer than the

[6] Lennander: Centralb. für Chirurgie, Feb. 23, 1901.
[7] E. Palier: New York Medical Journal, Sept. 16, 1899.
[8] J. L. Morse: Annals of Gynæc. and Pediatry, Nov., 1899.
[9] Mirande: Medical Press and Circular, June 5, 1901.

fourth day. The pain, rigidity, and sensitiveness of the abdominal wall cannot, therefore, be the result of a local, direct action of the intestinal lesion upon overlying tissues through pressure, contiguity of tissue, etc., but, instead, *the incidental expression of a general physiological function of which leucocytosis is an important attribute.*

That this is true is also sustained by the facts that the anatomical subdivisions of the peritoneum are purely arbitrary and that, as far as continuity of tissue goes, we are dealing with a single membrane. Unless the entire peritoneum be involved in the inflammatory process, therefore, the plea that the symptoms referred to are due to extension of the latter to its parietal or sensitive portion cannot hold. The cases in which cœliotomy reveals no signs of peritoneal inflammation notwithstanding the presence of these symptoms; the suddenness with which the latter may develop; the facts that they often appear before perforation has occurred and that the pain sometimes appears here, as in appendicitis, in spots quite remote from the area in which the lesion occurs, need only be mentioned to show that such cannot be the case.

Further evidence that we are dealing with a general process is afforded by the long list of diseases in which leucocytosis occurs and which includes, as already stated, all inflammatory disorders. Among the tissues which show a special predilection for diseases attended with leucocytosis are the serous membranes. Pleurisy, peritonitis, pericarditis, meningitis, etc., are familiar diseases in this connection. All are also accompanied by a more or less copious exudation of serum in which leucocytes, fibrin, and products of tissue-proliferation of the endothelial and connective-tissue cells prevail.

When, in the course of typhoid fever, perforation is about to occur, the fact that localized inflammation of the sensitive parietal peritoneum is not always found to account for the presence of leucocytes does not preclude the possibility of suddenly developed cellular overactivity manifested by enhanced cellular metabolism. Under these circumstances the sensitive parietal layer would be as markedly involved as the visceral. The pain and superficial tenderness would thus appear notwithstanding the total absence of sensation possessed by deeper

structures and merely because the parietal layer is supplied with nerves capable of transmitting pain-impulses. This would tend to suggest that the adrenal system might underlie the whole process, since increased activity of this system, brought on by a generalized infection originating in the intestinal ulceration (a toxin acting like any other poison), would correspondingly increase the oxyhæmoglobin ratio, and therefore enhance tissue-change and leucocytogenesis in proportion.

The effects of quinine upon the adrenal system will enable us to test this question. That this alkaloid produces upon this system effects similar to those caused by other sufficiently active drugs may readily be ascertained. In the stage of adrenal overactivity we have cerebral and peripheral congestion, manifested by headache, tinnitus, muscular agitation, convulsions, etc.; increased peripheral vascular pressure, shown by the flushed face, hæmaturia, spontaneous epistaxis, etc.; increased heart-action, shown by strengthened pulse-beat, with lowered frequency—sometimes down to 40, and other signs. When the stage of insufficiency is reached, great muscular weakness appears, followed by paralysis,—sometimes permanent in frogs,—lowered and depressed vascular pressure, with superficial anæsthesia; rapid and greatly weakened heart-beat; lowered temperature; dyspnœa, with lessened CO_2 elimination; methæmoglobinuria, etc. Five grains have been known to cause symptoms bordering on the latter stage. This is well illustrated by a case reported by Ciaglinski,[10] credited to "idiosyncrasy": a term which may become obsolete, since the special vulnerability which it serves to represent appears to be *due to functional impairment of the adrenal system.* The untoward symptoms occurred in a girl of 22 years, after a dose of only 5 grains. One hour after this was taken there suddenly developed agonizing præcordial and periumbilical pain, obstinate nausea, repeated vomiting and diarrhœa, with profuse, offensive stools of a black color. At the same time her body and extremities became covered with patches of urticaria. The rash disappeared spontaneously. The pulse was rapid, the pupils contracted, and there was marked tenderness of the

[10] Ciaglinski: Gazeta Lekarska, No. 13, 1892.

abdomen. A small dose taken some time before produced the same effect; morphine had likewise given rise to unusual symptoms. Adrenal insufficiency is also well exemplified in a case witnessed by A. E. Roberts.[11] The patient, a woman of 36 years, after taking about 300 grains, became totally unconscious and inert. The surface was cold and livid; the axillary temperature, 95° F. (35° C.); the respiration almost imperceptible, shallow, and slow; and the pulse thin and small. The pupils were considerably dilated, and did not respond to light. She vomited what the author terms "coffee-ground substance" several times. She recovered, but with impaired vision.

Taken collectively, all the symptoms of poisoning enumerated distinctly show that quinine is no exception in respect to the effects of drugs recorded in the second chapter, and yet we meet with ample testimony to the effect that this alkaloid checks the migration of leucocytes. At first sight, therefore, it would seem that the stimulation of the adrenals which quinine undoubtedly induces cannot be considered as the underlying factor of leucocytosis, and that the increment of tissue metabolism attributed to the adrenal overactivity supposed to account for the symptoms referred to has no part in their production. The experiments of Binz, Kerner, Cutter, Hare, and Martin[12] not only distinctly show the inhibiting effect of quinine upon leucocytes, but also that in sufficiently strong solution it may arrest their amœboid movement: the *sine qua non* of phagocytic action. Analyzed more closely, however, the question assumes another aspect.

Although these investigators were necessarily working in the dark as regards the governing influence of exact dosage, and the results reported thus lose much of their value for the present analysis, they nevertheless furnish many elucidative data. Binz, for instance, using the method of Cohnheim, curarized the frogs used for the experiment, so that the animals' adrenals were not only submitted to the influence of one toxic, but of two: curare and quinine. That the animals were already suffering from the effects of adrenal insufficiency when their mesentery was exposed upon the stage of the micro-

[11] A. E. Roberts: Lancet, March 9, 1895.
[12] H. C. Wood: *Loc. cit.*, p. 534.

scope is therefore probable. No accumulation of leucocytes occurred under irritation and, when after a time they began to accumulate, Binz at once checked them by a small hypodermic injection of the alkaloid: a normal consequence, if the adrenal insufficiency had anything to do with the production of leucocytosis. Again, Binz took two young cats, and, "after *poisoning* one of them with quinine," says Wood, "examined their blood. In the blood of the *unpoisoned* animal the white cells were far more abundant than in that of the poisoned cat." It is from these experiments that Binz deduced that quinine acted destructively upon leucocytes "in the same way as when they are out of the body." If the rôle of the adrenal system is what we deem it to be, the opposite is true: The poisoned animal did not show leucocytosis because its adrenal system had been rendered insufficient by the poison, while the unpoisoned animal showed marked leucocytosis because its adrenal system acted normally. As to the *extra corpore* effects of quinine upon the blood, the reader has doubtless already thought of their valuelessness if the adrenal system is the source of toxic symptoms.

It is probable that all the animals used for the experiments referred to were given sufficiently large doses to produce adrenal insufficiency. Only small animals were used, and, if we consider that 30 grains are sufficient to bring the adrenals of some normal adults unaccustomed to quinine to the brink of insufficiency, it is more than probable that the doses employed in the experiments far exceeded those capable of only bringing on the stage of excitement or overactivity. Wild, of all the investigators referred to by Wood, is alone stated to have used very weak solutions (1 part to 5000). In contradistinction to the contraction of blood-vessels noted by others, he observed "an enormous dilation of the vessels, with consequent increased rapidity of passage through them of liquid under pressure." The inference is obvious.

Hare's remarks, supplemented by Wood's deductions, are very interesting in this connection when the proposition submitted in the first chapter—"muscular vessels and capillaries are antagonistic in contraction and dilation" — is recalled. Hare, who had also been led to conclude that quinine prevented

"the extrusion of white blood-cells from the frog's mesentery," found "that the vessels in the cinchonized frog were much more contracted and had their walls much thicker than in a corresponding frog without quinine." Wood, on the other hand, says that "it is certain that the alkaloid reduces very markedly the force of the heart" and adds "it is therefore possible that the quinine prevents the outwandering by lessening the force which is driving the corpuscles and at the same time increasing the resistance of the capillary walls." It is evident that the contractions of these vessels witnessed by Hare would, if the foregoing proposition represents the actual mechanism involved, be the normal effect of toxic doses, while the "outwandering" of the leucocytes and the "resistance of the capillary walls" would occur as normal sequences of the process. Underlying it all appears the weak heart, suggesting that its normal stimulant had been reduced quantitatively through the inhibitory action of the alkaloid upon the adrenal system.

When all these features of the problem are collectively considered, it seems permissible to conclude that *leucocytosis, or at least the more or less prolonged exacerbations of this condition witnessed in various diseases, is the result of overactivity of the adrenal system induced by the toxins of pathogenic germs, poisons, venoms, products of metabolism, foreign substances, etc., when any of these penetrate the blood-stream in sufficient quantities.*

This not only accounts for the leucocytosis observed in disease and for that witnessed after active exercise, massage, etc.,—the so-called physiological leucocytosis,—but also for that due to the introduction of various drugs into the system: the so-called "medicinal" leucocytosis. The very existence of such a subdivision of the subject as the latter points to a common source for protective functions: one in which the adrenals play a commanding part, if the effects of drugs upon the adrenal system as depicted in this work at all obtain.

Further evidence is available in the literature upon the antitoxic effects of various serums. Besredka,[13] for instance, found that leucocytic serum produced effects that varied very

[13] Besredka: Annales de l'Institut Pasteur, vol. xiv, 1900.

greatly. While 3 or 4 cubic centimeters of a normal rabbit's serum killed guinea-pigs in a few hours, after these animals had shown *extreme hypothermia, diarrhœa,* and *collapse,* the necropsy revealing the presence of an *abundant limpid* and *sterile exudate in the peritoneum* with but few cells, *smaller* doses gave rise to *very abundant leucocytosis.* According to Schütze,[14] the steps of the process in guinea-pigs are as follows: At first a limpid fluid containing a few leucocytes is exuded; after about twenty-four hours an increase becomes manifest, while on the third and fourth days it becomes extreme (Besredka); after a second dose on the fourth day the count, from 17,500, gradually increased until 166,500 per millimeter was reached. This investigator attributes the stimulating effects observed to an action upon the leucocyte-producing organs: a correct interpretation, provided the adrenal system is included in the process. Indeed, we have submitted ample testimony to make it evident that the adrenal system, under the influence of toxics, at first increases, by its secretion, the oxyhæmoglobin in the blood, and correspondingly enhances all the functions of the organism. We can, therefore, legitimately conclude that *the activity of all physiological protective processes, including the elimination of toxics by the liver, and the production of leucocytes, i.e., of bactericidal cells, by the lymphatic system, the bone-marrow, and the spleen, is likewise enhanced when the adrenal system is overstimulated by poisons.*

Another feature of phagocytosis as a physiological function is embodied in the postulate—"muscular vessels and capillaries are antagonistic in contraction and dilation"—when all structures made up of endothelial cells, capillaries, serous membranes, etc., are included in the process. Phagocytosis, as conceived by Metchnikoff, is not limited to the polymorphonuclear neutrophilic, and other wandering leucocytes, but it also includes stationary endothelial and connective-tissue cells, which take up pathogenic organisms and foreign substances and disintegrate them, precisely as do the free cells. It also includes Kupffer's stellate cells, the pulp-cells of the spleen and of the bone-marrow. The quantity of living elements thus brought

[14] Schütze: Deutsche med. Wochenschrift, No. 27, 1900; quoted by W. Bulloch, Practitioner, May, 1901.

into protective activity is, indeed, suggestive when their extensive distribution is recalled. As is well known, endothelial cells line all spaces, channels, or cavities, large or small, that permeate the great connective-tissue system. The peritoneal, pleural, pericardial, and arachnoid cavities, the lymph-vessels, and the inner surface of blood-vessels are thus protected throughout with a complete layer of these elements.

Especially important is it to recall, in this connection, a few classic features, namely: that the capillary system is practically made up of endothelial cells joined edge to edge; that the circulation of the blood in these minute vessels is relatively slow; that the peripheral portion of the blood coursing through them, *that part in contact with their endothelial walls*, adheres, so to say, to the latter and is further delayed; and, finally, that serous membranes are, like the capillaries, endothelial structures. The peritoneum, the pleura, the pericardium, the meninges, etc., thus become *an extension of the capillary endothelial system*, and when, in the light of the doctrines advanced in this work, these serous structures and the capillaries are considered as one, we have constituted an extensive system of epuration, the physiological mechanism of which seems to us to be represented in the following summary:—

The blood-vessels, supplied with a muscular coat, when unduly contracted through the excessive functional activity of the adrenal system induced by toxics, force the blood into the peripheral capillaries, and, in some disorders, into those of serous membranes; all these capillaries, owing to their phagocytic endothelial walls and the wandering phagocytic leucocytes of the blood-plasma, thus become collectively transformed into a vast immunizing field.

It may prove interesting, in this connection, to refer to the importance of the capillary system as viewed by Claude Bernard[15] when compared to the balance of the vascular system: "The larger vessels, the arteries, the veins," writes this great physiologist, "are but streets which enable us to meander through a city; but with the capillaries we can enter the houses, in which we can directly study the modes of life, occupations, and customs of the inhabitants. Thus, when a toxic or medic-

[15] Claude Bernard: "Physiologie Opératoire," 1879; quoted by M. Duval, *loc. cit.*

inal substance is introduced into the circulatory tree, this substance will remain without effect as long as it will only circulate in the arteries and veins. It will only begin to manifest its activity on reaching the capillaries, and in them bathe the anatomical elements upon which it especially acts." As we view the process, of course, it is the toxic that is acted upon by the anatomical elements: the reverse, therefore, of Claude Bernard's view.

The application of our interpretation to Russel's typhoid-fever cases—the six in which details are furnished—may further serve to elucidate the whole question. Why did Mrs. V., Case III, die notwithstanding surgical intervention? On the sixteenth day of the disease her leucocyte-count showed 6100. Evidently the ulcerative process was already far advanced; the blood was markedly filled with pathogenic elements, and the adrenals were nearing the stage of insufficiency; hence the low leucocyte ratio. The prevailing view as regards the diagnostic value of leucocytosis in respect to perforation suggesting safety in this direction, it was only when the classic signs of perforation suddenly developed that cœliotomy was resorted to. The leucocyte ratio was then 4800: evidence that the adrenal system had lost ground. The patient died because the functions of this system had become so compromised by the toxæmia *that her entire vital mechanism, through the imperfect blood oxidation involved, had become correspondingly inadequate.* The toxæmia having overcome her adrenal system, the protective processes in the capillary, serous, hepatic, etc., cellular elements not only failed, but all her functions, including that of leucocytogenesis in the bone-marrow, spleen, etc., likewise. Briefly, *her adrenal system stood as the foundation of her life's mechanism, i.e., the underlying factor of her oxygen-taking powers and of her autoprotective functions, and dissolution followed when it failed her.*

Four of the cases submitted to operative procedures that showed a high leucocyte-count—namely: 28,000, 12,000, 14,500, and 17,000—recovered. The sixth case, however, showed a blood-count ranging from 12,000 to 14,000; but, operation being delayed, it reached 32,000. Why did this patient die? The very fact of the presence of so high a percentage points

to extensive toxæmia with *adequate* adrenals, but we have here an example of *excessive toxin-dosage.* The organs suddenly failed precisely as they did in the case of poisoning with 300 grains of quinine, and the symptoms of collapse of the one are those of the other. Since all poisons act similarly upon the adrenal system, *toxins must be similar to drugs in their effects upon the adrenal system.*

As to its diagnostic value in typhoid fever, leucocytosis being a protective process varying in degree (all things being equal) with that of the toxæmia, it fluctuates proportionally with the efficiency of the adrenals. We therefore have in leucocytosis, not a direct sign of impending perforation, but *a means of gauging the likelihood of perforation through the intensity of the ulcerative process as reflected by the toxæmia.* An excess of from 3000 to 10,000, therefore, points to a correspondingly active ulceration, which may at any moment bring on this complication, though the pulse show no unusual rise. Yet the leucocyte-count may reach 14,500, as stated by Cabot, and even far beyond, and perforation fail to occur. When, however, a high ratio is reached, another source of danger appears upon the scene: a more or less sudden inhibition of adrenal functions through excessive dosage of toxins. Finally, hypoleucocytosis may point, especially with a weak pulse, hypothermia, etc., to gradually increasing reduction of adrenal efficiency—all signs of a vicious circle that will soon end in death unless the focus of intoxication can be eradicated. These clinical features show that the views herein submitted are capable of standing the crucial test of practical application, and that *overactivity of the adrenal system is the inciting factor of leucocytosis and therefore of phagocytosis.*

Analyzed in the light of the foregoing statements, phagocytosis might possibly be made to subserve all the requirements of a function capable of protecting the organism against bacteria and other disease-breeding bodies. The endothelial lining of the pulmonary alveoli alone, for example, constitutes a potent barrier against the intrusion of pathogenic germs. The vast surface of phagocytes arranged in perfect battle-array, so disposed as to at once capture, ingest, and destroy any intruder as soon as he comes near enough to excite, by his own

chemotactic influence, a reaction in each soldier cell; the second line of free, mobile, phagocytic leucocytes in the plasma bathing the first line of defense, ever ready to pounce upon any single enemy who may have escaped the attacks of the first line; the vascular endothelial walls, built of phagocytic cells; the slowly moving, searching leucocytes in the plasma itself, able to send one or more pseudopodia through their stationary fixed kindred of the capillary walls, then pass into the neighboring lymph-spaces themselves, to reinforce, if need be, the connective-tissue phagocytic cells and surround the threatening germ; and finally the great cremator and eliminator, *i.e.*, the liver, constantly supplied with a quantity of oxidizing substance which no other organ, except the lungs, can approach —all constitute a system of defense wonderful in the extreme.

BUCHNER'S BACTERICIDAL ALEXINS.

What phagocytosis really means is but meagerly depicted in this brief summary of its rôle, and yet it is undoubtedly supplemented with functions calculated not only to afford even greater protection against disease to the cellular structures of which the various organs are built, but also to facilitate and insure the proper execution of all functions, organo-vital and protective. Indeed, the higher in the evolutive scale a living structure has reached, the greater seem the precautions taken by Nature to preserve its integrity.

A seemingly strong argument against phagocytosis as the only source of physiological immunity soon appeared after Metchnikoff's earlier labors became known: *i.e.*, the fact that various body-fluids—the plasma, exudates, etc.—were quite able to destroy bacteria without the presence of leucocytes. Thus, Pfeiffer,[16] having injected contaminated bouillon into the peritoneal cavity of guinea-pigs, found,—after withdrawing some at intervals of ten, twenty, and thirty minutes after the injection,—in the peritoneal fluids of these animals, motionless granules representing as many degenerated and dead bacteria. The peritoneal cavity containing but a minimum proportion of leucocytes, he failed to admit that this evident destruction

[16] Pfeiffer: Zeitschrift für Hygiene und Infectionsk., vol. xvi, p. 287, 1895.

of micro-organisms could be attributed to phagocytosis, and expressed the view, therefore, that the bactericidal power could only reside in the serum.

In the light of the functions herein attributed to the adrenal system, this conclusion might appear fallacious; but it is not so when reduced to appropriate limits. An important feature of suprarenal functions, in this connection, must be emphasized: *i.e., that their normal activity seems only to be heightened to a subjectively and objectively appreciable level when a certain degree of toxæmia has been reached.* In other words, the symptoms of which the adrenal system is the cause seem always to be due to the presence in the blood of poisons, venoms, toxins, etc., in sufficient quantities to defy the *normal* local cellular and humoral systems of defense. Hence the total absence of adrenal symptoms noted after the use of remedies when the dose administered is sufficiently small. And yet, if our views are sound, we are no longer dealing with the entire body as the basis of our estimates concerning the physiological action of drugs, but with a single organ: the anterior pituitary body. To this organ, *no larger than a small pea,* and its functional fluctuations, must now be ascribed a long list of general phenomena which we have all been taught to ascribe to the direct action of our remedies upon the blood and the tissues at large. It is this diminutive organ that all toxics of various kinds attack, but only provided they are allowed to reach it by the defensive cells and chemical bodies, with which, as we will see, the blood-plasma is amply supplied. But its protective offices are not called into use merely when toxics are ingested or introduced into the blood-stream by contamination; it is exercised at all times. We have in physiological leucocytosis evidence of this fact, for this phenomenon merely shows that after active physical exercise, a sufficient or copious meal, a cold bath, etc., waste-products of metabolism have accumulated in the tissues to an abnormal extent, and that the greater oxidation which unusual adrenal activity can procure has become necessary. This lasts as long as required, and the adrenals resume their relatively passive state. It thus becomes evident that the blood-serum is an important factor of the protective process.

Pfeiffer's conclusion that the bactericidal power resides in the serum, therefore, was not unwarranted, although the local leucocytosis—that available from the immediate surroundings through the chemotactic influence of the pathogenic germs introduced—might have sufficed to account for the destruction of the latter. Yet, how was the field so rapidly cleared of leucocytes as it was, and what was the origin of the granular *detritus?* Granting that the fluid did possess microbicidal properties, how could Pfeiffer explain the presence of bacteria within phagocytes, which presence he had himself witnessed? The fact that these organisms were dead led him to conclude that phagocytes were really only scavengers, and that they ingested dead bacteria after the serum had killed them. Hence, to the serum belonged, in his opinion, all the bactericidal power.

Metchnikoff,[17] while recognizing the strength of Pfeiffer's observations in respect to the ability of the peritoneal effusion to kill germs, showed that leucocytes capable of acting as phagocytes in the peritoneal cavity were accumulated in masses on the surrounding free surfaces, and that those damaged during the fray could easily be detected in the serous fluid if the latter were withdrawn in from two to six minutes after the injection. The colored plate opposite page 628 is interesting in this connection. Metchnikoff further showed that these damaged leucocytes were nevertheless able to destroy them by their secretions: a feature which explained the bactericidal property of the liquid. All these facts have since been demonstrated by a large number of experiments. The doctrine of phagocytosis has remained unassailed, . . . but so has Pfeiffer's view.

Denys showed that the bactericidal property of the serum increased or decreased according to the number of leucocytes present. Anthrax bacilli placed in small bags permeable only to the fluids of the blood and introduced into various bodily fluids were found to be dead when withdrawn. Metchnikoff and Bordet were led to conclude that this was due to the presence, in the blood-serum, of a substance, "microcytase," which was always found in plasma rich in phagocytes, and was invariably absent, however, when these cells were also absent.

[17] Metchnikoff: Annales de l'Institut Pasteur, June 25, 1895.

This feature was thought to point directly to the latter as the bactericidal agents.

EXPLANATION OF PLATE.—Fig. 1.—Pfeiffer's phenomenon occurring in the exudation taken from an untouched guinea-pig, the exudation having been withdrawn ten minutes after the injection of 1 cubic centimeter of bouillon containing one loopful of a culture of Constantinople cholera and 0.04 cubic centimeter of preventive serum (of the strength of $^1/_8$ milligramme). Staining with methylene-blue. *l*, Lymphocytes. Ocular 3. $^1/_{18}$ Zeiss.

Fig. 2.—Mass of granules placed around a collection of leucocytes. Exudation of a guinea-pig withdrawn nine minutes after the injection of 1 cubic centimeter of bouillon to which had been added a third of a culture of Oriental-Prussia cholera and 0.04 cubic centimeter of preventive cholera serum of goat (strength, 0.0002). Ocular 2. D. Zeiss.

Fig. 3.—Granular leucocyte surrounded by a zone of vibrionic granules. The exudation was withdrawn twenty-five minutes after the peritoneal injection of one-tenth of an agar-agar culture of Massowah vibrio. Ocular 2. $^1/_{18}$ Zeiss.

Fig. 4.—Two mononuclear leucocytes surrounded by granules; a lymphocyte (*l*) and a red blood-corpuscle (*h*) from the same exudation. Same power.

Fig. 5.—The same cells after remaining for three and one-half hours at 26°.

Fig. 6.—Five polynuclear leucocytes from the exudation withdrawn four minutes after the injection into the peritoneum of a guinea-pig (highly vaccinated and prepared with 3 cubic centimeters of bouillon) of 1 cubic centimeter of bouillon with one-third of an agar-agar culture of Oriental-Prussia cholera. *n*, Nucleus of a crushed macrophage. Staining with methylene-blue. Ocular 3. $^1/_{18}$ Zeiss.

Fig. 7. — Mononuclear leucocyte filled with Courbevoie cholera vibrios. Peritoneal exudation of a guinea-pig. Ocular 3. $^1/_{18}$ Zeiss.

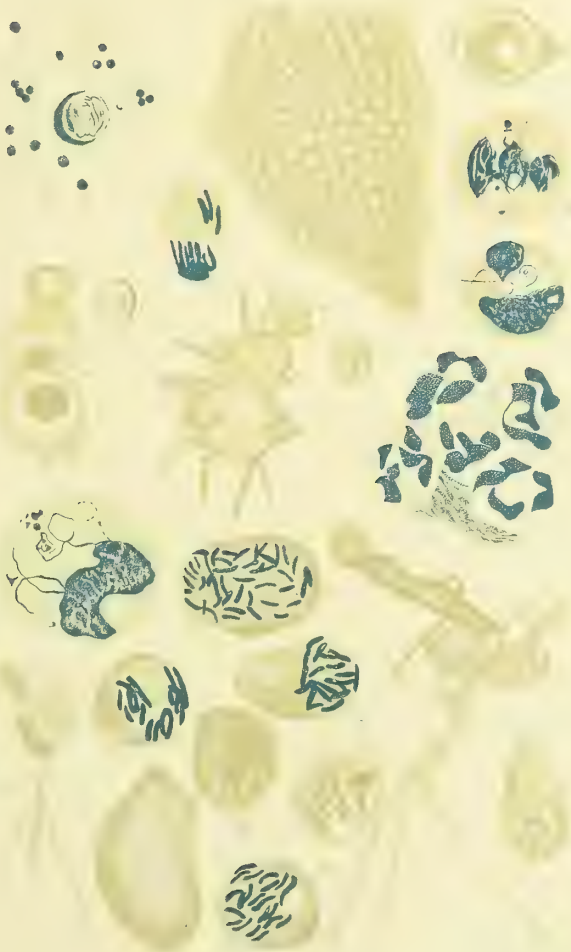
Figs. 8 and 9.—Two polynuclear leucocytes from the same exudation. The vibrios stained gray in the plate are vibrios in the eosinophile stage. Ocular 3. $^1/_{18}$ Zeiss.

Figs. 10 to 14.—Various phases in the formation of cultures of cholera vibrio (Oriental Prussia) within leucocytes. Hanging drop, stained with methylene-blue, of the exudation of a guinea-pig hypervaccinated for almost six months and prepared with 3 cubic centimeters of bouillon. The exudation was withdrawn four minutes after the peritoneal injection of one-third of an agar-agar cholera culture placed in 1 cubic centimeter of bouillon and kept at 38°. Ocular 3. $^1/_{18}$ Zeiss.

Figs. 15 to 18.—Various phases in the formation of cultures of the Kiel red bacillus within leucocytes. The hanging drop was kept for twenty hours at 17° and was made with the exudation from an hypervaccinated guinea-pig prepared with an injection of 3 cubic centimeters of bouillon. The exudation was withdrawn four minutes after the introduction into the peritoneum of the Kiel bacilli. Ocular 3. $^1/_{18}$ Zeiss.

Figs. 19 and 20.—Two consecutive phases of a culture of Kiel red bacilli grown from within a polynuclear leucocyte in a hanging drop of peritoneal exudation. The drop was prepared from the exudation of an hypervaccinated guinea-pig, withdrawn three hours and fifty minutes after the injection of Kiel bacilli into the peritoneum. *n*, Nucleus. Ocular 2. $^1/_{18}$ Zeiss.

Then came a series of investigations upon the antitoxic power of the blood and other liquids of the organism which appear to us to harmonize with the views of Metchnikoff and Pfeiffer. The most noteworthy were those of Hankin, von Fodor, and Nuttall, whose labors led to a doctrine of which



INTRAPHAGOCYTIC DESTRUCTION OF BACTERIA. *[Metchnikoff.]*

[*Annales de l'Institut Pasteur.*]

Buchner is the main exponent. According to this investigator, the blood-serum and body-fluids kill bacteria because they contain substances termed "alexins," which are thought to represent the secretory products of leucocytes. The effects of these alexins were found to vary greatly: under certain conditions they can overcome myriads of bacteria in a short time; under others their influence becomes practically *nil.* The loss of certain salts, for example, deprives them of their bactericidal property. This also occurs when they are diluted in ten times their volume of water, or when exposed at least thirty minutes to a temperature of 55° C. The addition of certain alkalies, however, enables them to preserve their properties up to 70° C. On the other hand, a brief exposure to the normal body-temperature, 37° C., causes them to become somewhat attenuated. More recently Laschtscenko,[18] working in Buchner's laboratory, found it possible to extract the bactericidal alexins from the leucocytes of rabbits without destroying these cells. It is evident, therefore, that, while leucocytes may act as phagocytes, they may also, while living, secrete a bactericidal substance. Metchnikoff's doctrine in respect to phagocytosis proper, and Pfeiffer's doctrine as regards the bactericidal powers of body-fluids, are thereby sustained, but with limitations, since it is clear that phagocytes are not mere scavengers and that they need not die to become poisonous to pathogenic germs. In fact, everything goes to prove that the phagocytic action and the alexinic destructive processes are carried on simultaneously: *i.e.,* that *the alexins given out by the leucocytes first weaken the bacteria,* and that *the latter are then ingulfed, alive or dead, by the phagocytes.*

As to the nature of the bactericidal substance, Buchner believes it to be a ferment capable of splitting proteids, and that it submits the bacteria to a process of digestion resembling, to a degree, the effect of blood-serum upon the albuminous constituents of blood-corpuscles.

If to the protective rôle of phagocytes in the system we now add alexins or substances secreted by each leucocyte and capable of weakening or killing bacteria, the protective rôle as

[18] Laschtscenko: "Transactions of the Thirteenth International Congress," 1900.

depicted a few pages back becomes enhanced. The epithelial cells of the pulmonary alveoli not only seize the pathogenic germ, but they are capable of further insuring their destructive work by first weakening their enemy with their secretion. If bacteria penetrate the first line of defense, they meet not only the free leucocytes beyond, but their alexins. It is when, if still active, they become engaged in the capillary net-work, however, that bacteria undergo their greatest exposure. Indeed, both the fixed and wandering leucocytes and their secretions are all crowded together in these vessels,—or bactericidal channels,—and the pathogenic organisms, dragged along by the blood-stream, must indeed be numerous to overcome the defensive hosts placed across their path.

If the toxic products of the bacteria in the blood exceed a given limit, adrenal overactivity is awakened. An influx of blood in the entire capillary system ensues, bringing along with it a steadily increasing array of phagocytes, each endowed with its poisonous atmosphere and capable of ingulfing a large number of bacteria. Veins and venules, arteries and arterioles, by responding through the muscular fibers in their walls to the suprarenal impetus, lock up, as it were, the offensive and defensive host together on the field of action,—*i.e.*, the capillaries, the fluids in the connective tissue, lymph-spaces, etc.,—and, "muscular vessels and capillaries being antagonistic in contraction and dilation," the latter are dilated through the greater quantity of blood forced into them, and the efficiency of the defensive processes is rendered all the more efficacious. The heart-beats are slower, but firmer and stronger; the surface of the body, replete with capillaries, is flushed and hot, the temperature rises, etc. Briefly, all the signs of adrenal overactivity, *i.e.*, *fever*, appear, and continue until the pathogenic organisms present are overcome.

All diseases would end favorably in a previously healthy subject were bacteria alone to be contended with. But the time has long passed since micro-organisms were considered as the pathogenic factors *per se* in the diseases in which they are found. Precisely as leucocytes secrete or produce alexins, so do bacteria produce toxins. In fact, as is well known, bacteria need not enter the general circulation at all and still produce

disease. Diphtheria and tetanus, for example, typify a class of affections in which toxins alone enter the blood, in contradistinction to cholera, typhoid fever, and other maladies in which the bacteria penetrate into the circulation and there develop their toxins. Snake-venom, mineral and vegetable poisons, etc., represent other classes of agents in which no bacilli enter the blood and which must meet therein counteracting influences. On the whole, it appears evident that there must also exist some means or property in the body through which the effects of the specific toxins produced by pathogenic organisms, snake-venoms, and poisons of all kinds are antagonized.

Buchner expresses the belief that the proteid-splitting ferment secreted by leucocytes and that secreted by pathogenic bacteria may be similar, and refers to Hahn's experiments,[19] which showed the presence of these ferments not only in yeast-cells, but also in the typhoid and tubercle bacillus. It seems evident to us that such cannot be the case. The alexins secreted by leucocytes and bacteria being similar and *mutually* destructive, these cellular structures would become *auto*destructive. In other words, a leucocyte under such circumstances would be creating a substance for its own destruction and so would the pathogenic germ. No protective process would, therefore, prevail. When germs and leucocytes would meet in a given region,—the interior of a capillary, for instance,—all structures vulnerable to the alexins or proteolytic ferment—leucocytes, bacteria, red corpuscles, the capillary walls, etc.—would be sacrificed. Indeed, Buchner accounts for the breaking down of abscesses in this manner. But it seems clear that, if applicable to a limited area, the destructive process should also prevail when in general affections the entire capillary system is replete with leucocytes and bacteria, and that, as a result also prevail when in general affections the entire capillary system would also be sacrificed. Briefly, the similarity between the bacterial and leucocytic alexins might stand analysis were it applicable only to strictly localized morbid processes involving but a very limited area, but it is inadequate when applied to

[19] Hahn: Münchener med. Wochenschrift, Sept. 26, 1899.

general affections. Again, the blood in severe cases of septicæmia and cholera literally teems with bacilli: living evidences that the phagocytes, notwithstanding their destructive powers, physical and chemical, over bacteria, have failed in their protective functions. This vast accumulation of pathogenic germs in the blood-stream necessarily involves the production of quantities of toxin. Even admitting the possibility of autoexhaustion, how could, under such circumstances, any bacilli-ridden and toxin-saturated patients ever survive? We might invoke the potent assistance of the adrenal system and through this a steady outpour of leucocytes, an inordinate degree of hepatic and general cellular activity, etc. But we must not overlook the destructive effect which suprarenal overactivity would thus involve, since the adrenals would then be urging the production of so-called protective cells, which, as soon as they would reach the field of action, would not turn their whole offensive energy against the pathogenic organisms, but contribute to the latter's efforts in seeking general destruction!

Quite another position is assumed by Buchner's alexins, however, when they are considered only as leucocytic products functionally associated with Metchnikoff's phagocytes and Pfeiffer's bactericidal serum. In fact, it is probable that the latter owes its properties to Buchner's alexins; it appears to us that as far as the destruction of *bacteria* is concerned, phagocytes and alexins satisfy all the needs of the organism. Not so, however, with the bacterial toxins; nothing, so far, seems to have furnished a clue to the manner in which their virulence is antagonized in the blood-stream. This question will be taken up later on.

THE ADRENAL SYSTEM AND THE VULNERABILITY OF CHILDREN TO INFECTIOUS DISEASES.

We can reasonably surmise that the tissue-cells are not provided with a special line of defense for each kind of poison, and that all are, in a general way, submitted to the same physico-chemical antagonism when introduced into the body. The effects, we now know, vary with the dose, whether it be a toxin or any other poison; but we also know that the same dose may prove much more active in one individual than in another.

Drug and dose being identical, we can only incriminate the protective process, and we are thus led to inquire into the causes that may militate against phagocytosis and against the formation of sufficient alexins to maintain the serum up to its highest degree of efficiency.

The relationship between the production of leucocytes and adrenal overactivity has already been shown. In disease the symptomatic concordance is such as to eliminate all doubt that *the increased blood-oxidation incident upon adrenal overactivity is the underlying factor of leucocytosis, and therefore of phagocytosis.* The difference between the effects of similar doses in different individuals has also been referred to; we have seen that "idiosyncrasy," or abnormal sensitiveness to the effects of drugs, is easily explained by the reduced resistance that disease or functional impairment of the adrenal system involves. The frequency with which the adrenals are the seat of fatty degeneration has been emphasized by Arnaud and Rolleston. We have also seen to what extent they react to the effects of drugs, and that any local disorder brings them nearer the stage of insufficiency in proportion as the lesion is profound. We may thus not only have varying degrees of sensitiveness to the effects of drugs, but, for the same reasons, we can also account for the variation in our resistance to disease. *Impairment of the functions of the adrenal system involves a corresponding loss of resistance to the effects of toxics of all kinds,—toxins, poisons, venoms, etc.,—because this system governs the intensity of the oxidation processes and, therefore, nutrition.* Such being the case, *phagocytosis and the production of alexins, when inadequate, but reflect a corresponding impairment of the adrenal system.*

The far-reaching meaning of this relationship between the adrenals and the physiological protective processes soon becomes apparent when the results of the varying degrees of adrenal insufficiency are considered. Most prominent among these is the predilection of children to infectious diseases. If experimental evidence is to be taken as standard, Ehrlich's experiments with ricin, abrin, and robin upon mice, supplemented by those of Wernicke, Hünener, and Vaillard, clearly indicate that his conclusion that immunity is not conferred by

parent to offspring must prevail. Ehrlich has also shown that the offspring can acquire immunity from its mother through the placental circulation—*i.e.*, from the mother's blood—and through her milk.

Immunity is not conferred, therefore, through the germinal cell by the spermatozoa or by the ovum, but through a medium, the blood or milk, which contains the antitoxic element, whatever that may be. Yet these two sources of immunity, if the adrenal system is at all concerned in the process, must be considered as differing totally one from the other etiologically. Indeed, in respect to the influence of the maternal blood, *i.e.*, the placental circulation, the human fœtus is merely a part of its mother precisely as is one of her organs. The fœtal adrenal system undergoing development, its usefulness as a protective agent is therefore inhibited. In fact, the fœtus may reach maturity notwithstanding the total absence of these organs.[20] As to the influence of maternal milk, which is given the child when it has to depend upon its own protective resources,—*i.e.*, after birth,—we are simply in the presence of a process through which a *physiological antitoxic serum* is administered and *the immunizing attributes of which are communicated to the child.*

In our analysis of the physiology of the mammary gland (page 289) we referred to the fact that the liquid portion of milk was, in the main, blood-plasma, containing, therefore, oxidizing substance. We may now, it seems to us, add Buchner's alexins to the list of its constituents.

Analysis of the pathology of the adrenal system during early life also points to deficient protection from the adrenal system. From the observations of Leconte, Rolleston, Mattei, and his own, Arnaud was led to conclude that 46 per cent. of cadavers showed lesions in the adrenals ranging from slight hyperæmia to disruptive hæmorrhage. A comparative study of the 100 cases of suprarenal hæmorrhage collected by this author, however, shows that the *newborn alone* make up 45 of the 46 per cent. referred to, so that childhood, adult age, and old age are only represented by the remaining 1 per cent. The

[20] Winckel: "Transactions of the Thirteenth International Congress," 1900.

inference is obvious: This remarkable predilection of the newborn *exactly coincides with the moment at which the adrenals assume their protective functions,* which functions had been previously carried on by the mother's adrenals during the fœtus's uterine life.

If we now consider the fact, emphasized by Arnaud, that "suprarenal hæmorrhages are far more common in childhood than in adult or old age," we are led to another important deduction: This predilection to suprarenal hæmorrhage in children *coincides with that during which they show vulnerability to specific infectious diseases:* the so-called diseases of childhood especially.

Turning to the rarity of hæmorrhage in adult and old age, we are brought to realize that complete development of the adrenals brings with it almost complete immunity to certain toxins, especially those generated in the course of certain diseases of childhood. That this is true was demonstrated by a personal analysis of 42 cases of fatal suprarenal hæmorrhage in adults and old age found in literature. *Not one* of these could be traced to an infectious disease to which children are particularly liable. Local or remote chronic processes, tuberculosis, cancer, Bright's disease, etc., or processes attended with sudden and severe toxæmia, burns, traumatisms, uræmia, pneumonia, hepatic abscess, leg-ulcer, and cardiac affections were the only disorders found.

On the whole, the conclusions which seem to be warranted in this connection are the following:—

1. Children are vulnerable to certain infectious diseases, because their adrenal system is insufficiently developed, and thus fails to adequately stimulate the organs upon which the immunizing process depends when toxins penetrate the blood-stream.

2. Normal adult and old subjects are not vulnerable to the diseases of childhood, because their adrenals are developed sufficiently to enable them to correspondingly stimulate the organs upon which immunity to these diseases depends.

THE ADRENAL SYSTEM AND THE TUBERCULIN TEST.

Another question which the functional relationship between the adrenals and the physiological protective processes

seems to elucidate is the *modus operandi* of tuberculin in Koch's tuberculin test. Why does fever appear when this substance is injected only (it might be more proper to say "mainly") in individuals who are suffering from tubercular disease? Why is it also harmless for healthy animals, but violently toxic for tuberculous animals, going so far in these sometimes as to produce death? A rise of 2° F. or more above the normal temperature is brought about in tuberculous subjects, but if another injection be made within a period covering sometimes as much as two months, a reaction is not to be obtained. In the light of what has previously been said as to the predilection of the adrenals *per se* for tuberculosis, as observed in connection with Addison's disease, it seems probable that these organs must always be more or less organically diseased in any but the earliest stage of practically all cases: a complication which would explain the failure of Koch's tuberculin. Even leaving out of all consideration this important element of the tubercular process and considering the pulmonary, glandular, osseous, etc., lesion that may be present as the only pathological existing condition, the symptoms caused by the injections of tuberculin seem easy of explanation.

In the healthy subject the glands are in their normal functional state and the dose of tuberculin introduced into the circulation is insufficient to cause them to assume unusual activity. In the tuberculous subject, on the other hand, the diseased area is the source of toxins of various kinds which are constantly stimulating the adrenals to unusual activity. The dose of tuberculin does not alone under these conditions enhance suprarenal activity, but it represents an *addition* to the kindred toxin present; united, tuberculin and poison thus give rise to an exacerbation of the glandular functions which becomes manifest by the febrile state induced and other symptoms of adrenal overactivity.

Spurred to unusual energy by the tuberculin, the adrenal system excites correspondingly active metabolism in all cellular structures, including those endowed with leucocytogenesis. Phagocytes and alexins are produced in profusion, the fixed endothelial and the connective-tissue cells contributing their share to the production of the latter, and there is thus con-

stituted a serum which confers upon the treated individual a degree of immunity commensurate with the degree of the reaction produced in the adrenals—provided these organs are not seriously involved in the tuberculous process. It is, therefore, probable that *Koch's tuberculin gives rise to a febrile reaction when a tuberculous process is present, because it adds to the toxic elements incident upon the disease a new source of adrenal overactivity.*

THE ADRENAL SYSTEM AND ANTITOXIC SERUM.

We have considered so far but two of the means afforded by Nature to protect the body against infection. If, however, the foregoing illustrations of the relationship between adrenal functions and immunizing processes are closely analyzed, it soon becomes apparent that phagocytosis and Buchner's alexins—including those generated through the death of leucocytes and other globulins, endothelial cells, etc.—do not, as already stated, fully satisfy the needs of the situation. That these agencies are capable of destroying bacteria is undoubted. Behring found that the sterilizing effects of sheep's serum, for instance, were far greater than those of the stronger solutions of bichloride of mercury and carbolic acid employed in surgery; we have also seen that the strength of the serum, as shown by Denys, increased with the proportion of leucocytes contained therein. But how are bacterial *toxins* antagonized?

Whether there exists in the body a physiological antitoxin or antitoxic bodies capable of destroying bacterial toxins still belongs to the domain of conjecture. The very need of Ehrlich's ingenious side-chain theory points to this. In this hypothetical conception each body-cell is even more complex than we now deem it to be, and is supposed to be surrounded by various groups or chains of atoms which Ehrlich terms "toxophoric atoms"; these would possess a specific affinity for, and would unite with, toxins. The reaction involved would necessarily cause the production of bodies that would be useless to the cell and therefore be cast off. While the "toxophoric atoms" would be replaced in the cell, the bodies cast off from the latter would remain in the blood, and being still possessed of considerable affinity for toxins, they would constitute in the

blood what we term "antitoxin." The evidence mainly consists of the results of experiments *in vitro*, in which the affinity of various tissues for toxins are shown. Thus, if to an emulsion of brain or spinal cord in a salt solution there is added a dose of tetanus toxin sufficient to kill ten rabbits, the toxin will lose its power and prove harmless when injected into a single animal. Evidently there must have existed in the tissues thus used some substance capable of converting the toxin into an inert body.

Analysis of Ehrlich's theory, however, seems to us to show several vulnerable points. In the first place, we are called upon to conclude that the protoplasmic cells are so constituted as to be prepared to meet each individual toxin in a special manner. In other words, there must be as many side-chains or groups of "toxophoric atoms" as there are toxins. If we survey the field of pathology, the number of toxins so far isolated will already appear quite large; if we add to these what toxins may yet be discovered, we cannot but conclude that the cells of which our tissues are built must indeed be complex bodies if the hypothesis proves to represent facts. Again, a preconceived antenatal arrangement of the molecular elements of the cells with adjustment to the needs of existence in disease-ridden communities becomes necessary. Hertwig's view that acquired characters are transferable to the germ may serve to establish a connection between the development of the lateral atom groups and the numerous diseases to which the innumerable generations have been exposed in the past. But, as previously shown, experimental evidence, to which Ehrlich himself has contributed the most convincing data, tends to prove the contrary: *i.e.*, that immunity is not transferred to progeny through the germinal cell.

Again, Metchnikoff, Roux, and other bacteriologists have studied Ehrlich's hypothesis experimentally. Perhaps the most striking of these is the repetition of Ehrlich's own and Wasserman's experiments, but followed by controlling experiments in which carmine was used instead of brain and spinal-cord substance. Notwithstanding the substitution of this inert substance, however, the results were similar, the toxin being likewise rendered harmless by the carmine solution. It seems

evident, therefore, that the side-chain theory does not account, *in its present form,* for the protective phenomena witnessed and that the solution of the problem must be sought elsewhere.

The properties of the pathogenic agents may furnish a clue. Beginning with organic poisons, it is desirable to fully realize their identity as albuminoid bodies. This is demonstrated by their common tendency to lose their toxic powers when heated to 100° C.[21]—likewise a characteristic of snake-venom, as shown by Weir Mitchell and Reichert many years ago. Venom not only responds to all the tests that denote its albuminoid character, but so do toxins and the toxic bodies of plants: ricinus, jequirity, etc. Again, the relationship between these toxalbumins and vaccine substances is very close. Protective inoculation against small-pox may, as shown by Bertrand and Phisalix,[22] be imitated for snake-venoms. These facts not only reaffirm that all organic poisons, whatever be their source, must be treated collectively as regards effects, but they also show that *they are all vulnerable in the same manner, through the similarity of their molecular structure, to the physical agencies present in the organism that tend to convert them into harmless bodies.*

How are poisons converted into harmless substances?

A striking feature of the introduction of venom into the circulation is the loss of its identity as such. The poisoned blood may be removed from an animal in the throes of toxic manifestations of poisoning and injected into another, but normal, animal and produce no effect whatever. This was observed by Laborde in 1875 and confirmed by Calmette, who found that even an emulsion of the organs of the poisoned animal produced no effect upon a normal animal of the same kind. Similar results were obtained from hypodermic injections of cobra-poisoned blood taken from the heart, spleen, brain, and bulb, into the pigeon, rat, guinea-pig, and rabbit. Bufalini[23] injected 30 cubic centimeters of blood, taken from the vena cava of a man who had died as a result of a viper-bite, into the peritoneal cavity of a guinea-pig, but no untoward effects

[21] A. Gautier: "La Chimie de la Cellule vivante."
[22] *Ibid.*
[23] Bufalini: Quoted by Romiti, Archives ital. de Biologie, 1884.

were noted. Even the transfusion of *all* the blood of a dying scorpion-poisoned dog into the vessels of a bled dog caused no serious symptoms, according to Paul Bert.[24]

What is the nature of the process through which this is accomplished? It cannot be due to the smallness of the doses employed, since it was the aim of the investigators named to test the question: a fact, in itself, suggesting the use of large quantities of poisonous blood. Again, the toxicity of viper- and cobra- venoms, as previously shown in connection with blood-changes, is exceedingly high. The benign effects were doubtless due to the attenuation to which the venom had been submitted. It is evident that, since the latter had, in each instance, already passed through one animal, it had lost much of its virulence. The dose injected or transfused was, therefore, in no way comparable to the dose received in each case by the first subjects so that, quantitatively as well as qualitatively, it proved *insufficient to create an adrenal reaction capable of giving rise to symptoms of poisoning.* This confirms the need of a sufficiently great dose of a sufficiently virulent poison to bring about such active phenomena.

An important point is emphasized by the last of the experiments mentioned, Paul Bert's: The transfusion of all the blood of a dying scorpion-poisoned dog into the vessels of a bled dog means that the latter animal must have been bled to a sufficient degree to admit *all* the blood of the dying dog; in fact, that the greater part of the blood of the former dog—even if a larger animal than the scorpion-stung one—must have been removed. We therefore have practically an exchange of blood. The animal that received the poisoned blood having suffered no serious symptoms, it follows *(1) that the scorpion-venom could not have disorganized this blood: i.e., caused direct "hæmolysis"; (2) that, on the contrary, it was the blood which had disorganized the venom.* It is obvious that, had the blood of the first dog been injured chemically or morphologically to any marked extent, the second dog would not have fared as it did.

We are thus again made to fully realize the important fact,

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[24] Paul Bert: Société de Biologie, August 8, 1885.

and in opposition to classic teachings, that poisons do not exert their destructive action directly upon the blood, and that in our analysis we must consider all the acute symptoms of poisoning which appear to belong to the domain of the adrenal system alone as a separate entity: *i.e.*, a symptom-complex with which "blood-destruction," or "hæmolysis," is not concerned as a causative factor.

The question has now become simplified. We have not only eliminated the hæmolytic property from all poisons,—venoms, toxins, alkaloids, etc.,—but, recognizing the unity which all these destructive agencies undoubtedly show, we have reduced the working elements of the inquiry to two approximately known quantities, *blood* and *toxic*,—which we can now transform into blood *versus* toxic, and study as independent, though mutually related, propositions.

A general function betokens a broad principle of action. Not only must such an attribute exist, but, as the function in question is one directly connected with the preservation of life, it must be a predominating one.

Is there such a predominating attribute in the physical make-up of serum proper? That blood-serum is a mere menstruum has been repeatedly shown. Even the normal serum of animals that are naturally refractory to certain toxins was found by Calmette,[25] for example, to have no influence whatever upon those toxins *in vitro*. Of course, this only refers, as regards physical effects, to an animal's own serum or to that of animals in which it possesses kindred chemical properties. The serum of a particular species possesses physical properties peculiar to that species, and when used in others in which the constituents vary quantitatively it may produce more or less marked cytolysis, which may culminate in death. Thus, the venous transfusion of a small quantity of a normal dog's serum into a rabbit will soon prove fatal: the dog's serum is simply not adapted structurally to the globulins and other bodies in the rabbit's serum. This fact in itself furnishes evidence that blood-serum is a mere vehicle, and that what antitoxic bodies are contained in it are foreign to its own composition as serum.

[25] Calmette: Annales de l'Institut Pasteur, vol. x, 1897.

What is the nature of these antitoxic bodies? Or, in other words, what is "antitoxin"?

The source of "antitoxin" has not been traced to any particular organ or set of organs. All that is positively known is that in immunized animals—*i.e.*, animals into which toxins have been injected in gradually increased doses—it appears in the blood in constantly increasing quantities. In other words, its relative quantity is constantly changing, and it fluctuates with the quantity of toxins introduced into the circulation of a given animal.

That the toxins injected into animals to obtain antitoxic serum for purposes of immunization act on the adrenal system precisely as do other poisons needs hardly to be emphasized. When diphtheria *toxins* are injected, for instance, a feature of the earlier period of the treatment is the tendency to paralysis, which is often followed by rapid death. This association between paralysis and sudden death is very suggestive when we recall the influence of powerful toxics on the adrenals, and the induction of paralysis as an advanced symptom of the stage of insufficiency. Again, each injection causes a marked reaction, attended with a rise of temperature which sometimes reaches several degrees. As the doses of toxin are very gradually increased, it takes months to bring the animal's serum to the immunizing standard: *i.e.*, to that state when it contains, in a given quantity, a sufficient amount of *anti*toxin to confer immunity when that given quantity is injected into unprotected animals or human beings.

At the end of these months, however, an important change in the resistance of the animal to the poisonous effects of the toxins occurs: it is able to stand several hundred times the dose of toxin that would have proven fatal at the start. Ehrlich's experiments with abrin, the toxalbumin of the jequirity-bean, and ricin, that of the castor-bean, have shown that immunity to their poisonous effects could be conferred precisely in the same way. These purely vegetable poisons, in other words, not only behave as do toxins, but treatment of animals in the manner depicted above produces similar results, even to the extent of conferring immunity. Snake-venom again affirms its kinship to toxins and vegetable toxalbumins by

conferring equal protection. Calmette, Phisalix, and Bertrand, by treating animals as above, have obtained an *anti*venin which, injected into vulnerable subjects, protects them, as do *anti*toxin, *anti*abrin, and *anti*ricin, against its own deleterious effects.

A feature common to all animals so treated, however, is their tendency to "oversensitiveness" to the effects of the injections, active—and usually fatal—symptoms of acute poisoning appearing suddenly in the midst of apparent health. If this phenomenon is added to the adrenal signs already noted, we are strikingly reminded of the critical stage of adrenal overactivity and the sudden lapse of the glands into total inactivity. The gradual habituation to the toxin, the vegetable toxalbumin and the venom, furnishes complementary evidence as to the implication of the adrenal system in the process, typifying as it does that observed in arsenic eaters and in such conditions as morphinism, cocainism, etc. Indeed, it seems obvious that the gradually increased injections do what all other poisonous agencies do: *i.e., they gradually increase and simultaneously develop the functional activity of the adrenal system.*

This peculiar oversensitiveness to the effects of toxins and other interesting features of the problem that will assist in elucidating the question in point are referred to by Joseph McFarland,[26] as follows: "The occurrence of antitoxin in the blood-serum is to be considered as a phenomenon of forced immunization. During the immunization process it does not seem to develop in proportion to the toxic endurance of the animal, but, as Roux has pointed out, is rather suddenly developed after the immunization has attained a high degree. During the continuance of the immunization it is a variable, not a fixed quantity, and while the toxin endurance of the animal is kept up without variation, the antitoxin may gradually diminish. This I have seen many times illustrated in horses producing diphtheria antitoxin, an excellent illustration being afforded by one particular horse that furnished at one time a serum containing 1400 units to each cubic centimeter of serum. The immunity was maintained by cautious toxin injections for

[26] Joseph McFarland: "Text-book upon the Pathogenic Bacteria"; edition, 1900.

a long period subsequently, and the endurance of the horse remained unchanged for months, but the antitoxicity of its blood gradually declined, until from 1400 units it fell to 100 units.

"This rather sudden appearance of the antitoxin and its decline during the immunity of the animal prepare us for the information that the animal's immunity does not depend upon the antitoxin, but upon some other condition. The probable proof of this is seen in the peculiar condition of hypersensitivity to which Behring and Wladimiroff called attention, and of which mention has been made. In these cases it makes no matter how much antitoxic strength is contained in the blood, the animal is just as sensitive to the toxin as if it had none, and as if it had not been immunized. Moreover, the hypersensitivity is not a cumulative action of the toxin that outweighs the antitoxin, as will be readily shown by a simple calculation. A horse weighing 1300 pounds, possessing about 100 pounds of blood, of which about one-third, or 30 pounds, is serum, has been immunized to diphtheria toxin according to the method described in the chapter upon 'Diphtheria'; and while the serum contains 500 immunizing units of antitoxin in each cubic centimeter of blood-serum, the horse falls into the hypersensitive condition and dies. What relation exists between the antitoxin in its blood and the toxin that produced death?

"It is certain that there is *none,* and that the antitoxin that exerts a most remarkable protective influence upon other animals does not protect the animal by which it is formed.

"If the horse's blood furnishes a total of 30 pounds of serum, each pound being about equal to 500 cubic centimeters of liquid, there is a total of 15,000 cubic centimeters of antitoxic serum in the horse.

"Suppose the minimum fatal dose of diphtheria toxin for a 250-gramme guinea-pig to be 0.0045. If the serum under consideration contain 500 units in each cubic centimeter, then $^1/_{50000}$ cubic centimeter will protect a guinea-pig against 0.0045 cubic centimeter of the toxin; $^1/_{5000}$ cubic centimeter against 0.045 cubic centimeter; $^1/_{500}$ cubic centimeter against 0.45 cubic centimeter; $^1/_{50}$ cubic centimeter against 4.5 cubic

centimeters; $^1/_5$ cubic centimeter against 45 cubic centimeters; and 1 cubic centimeter against 9 cubic centimeters of the toxin. If each cubic centimeter of the serum of this horse is capable of destroying the toxic effect of 9 cubic centimeters of toxin, the total toxin-annulling capacity is 9 × 15,000 cubic centimeters of serum in the horse's blood = 135,000 cubic centimeters of toxin.

"We must next see how much toxin has been received by the horse during his immunization. The following doses, the figures referring to cubic centimeters of toxin, probably represent an average careful manipulation extending over a period of about three months: $^1/_{10}$, $^1/_4$, $^1/_2$, 1, 1, 2, 3, 5, 8, 10, 15, 20, 25, 50, 50, 100, 150, 200, 250, 300, 500, 500, 500, 500, making a total of about 4200 cubic centimeters of diphtheria toxin. Now observe that the total quantity of toxin consumed by the horse is 4200 cubic centimeters, but his protective energy is 135,000 cubic centimeters of toxin, so that the blood of this horse, if drawn from his body, would furnish enough protection to save 32 $^1/_7$ horses from doses of toxin as large as the total amount administered to him during the entire course of his treatment.

"This illustration is not only extremely instructive in showing the paradoxic nature of the condition of hypersensitivity, but certainly proves that the antitoxicity of the blood is not the cause of immunity, but a phenomenon of that state. It is also of great importance in considering the origin of the antitoxin.

"Concerning the origin of the antitoxins, we must at once dismiss from our minds the thought that bacteria have anything to do with their formation other than through the toxins they generate. The immunization of animals to feebly toxic cultures, or to bacteria washed of their toxins, produces immunity; but immunity without antitoxic activity produces the antimicrobic power of the blood presenting itself in these cases. It is, therefore, the poison alone that is responsible for the phenomenon, and a moment's reflection upon the anti-bodies produced by immunization to ricin, abrin, venom, eel's blood, etc., will clearly establish this fact. How does the poison produce the antitoxin?"

After reviewing the various hypotheses that have been proposed—that the antitoxin is the toxin itself, but in a modified form; that it is an enzyme produced in the culture; that it is a product of cellular activity—McFarland concludes, in accord with the prevailing opinion, that "probably the best explanation of the histogenesis of the antitoxin" is Ehrlich's lateral-chain theory. Indeed, some of the points made may be adduced as evidence in favor of the latter. The phenomena observed in the horse that furnished serum containing 1400 units, then 100 units, may be explained, for instance, by the exhaustion of cataphoric atoms: a feature of the process which simultaneously suggests its dependence upon the body-cells for the formation of the antitoxin. Yet, while the same reasons are applicable when the adrenal system is brought into the process,—suggesting at the same time that normal adrenals can produce a large amount of secretion, then become weakened without lapsing into sudden insufficiency,—it is difficult, with Ehrlich's theory, to account for the sudden sensitiveness observed, without indulging in pure conjectures based upon hypothetical deductions. The overwhelming evidence adduced as to the tendency of the adrenals to suddenly cease their functions and give rise to symptoms similar to those observed in the injected animals, on the other hand, the sudden deaths in Addison's disease, those that occur as the result of hæmorrhage into the adrenals, etc., emphatically point to adrenal insufficiency as its source. Adrenal insufficiency here obviously means that the oxidizing substance is a main factor of the entire process.

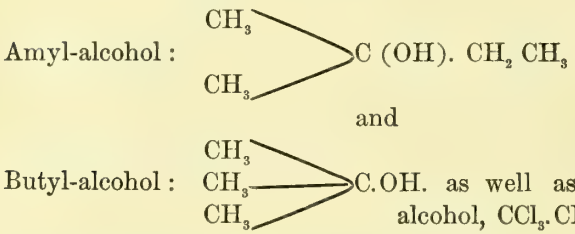
Indeed, that the presence of the oxidizing substance in the blood-serum accounts for a large number of reactions the nature of which has not, so far, been satisfactorily explained, seems undeniable. The long list of chemical agents which have been shown by Schmiedeberg, Salkowski, Jaquet, Langlois and Biarnés, among others, to be oxidizable through contact with various tissues and blood-serum represents but a diminutive proportion of the bodies that can be converted through a similar process into dissimilar compounds. Uric acid, we have seen, is the end-product of a series of reactions of this kind: a benign agent developed by oxidation from toxic

bodies of the purin group. Phosphoric acid must be a product of a similar kind, since, like uric acid, its excretion fluctuates under the influence of certain drugs, quinine, for instance (Kerner). Thyroid extract, as is well known, increases metabolic activity through the adrenal system, as we have seen, and simultaneously augments phosphoric-acid elimination. Arsenic does likewise and increases, as does thyroid, excretion of urea: evidence of overactivity of the adrenals induced by the toxic.

The vast field covered by oxidation processes in the organism, apart from those connected with cellular function, is well illustrated in the following quotation from an article by J. W. Wainwright[27]: "In the body itself organic drugs, like other chemical bodies, are either fully oxidized and burned to carbonic acid and water or urea or else a slight chemical change results in the molecule, in which the annular grouping of the nuclei is preserved. Besides, the organism possesses the ability to bring about syntheses, and in this way hamper or abolish the action of drugs to a certain degree. Our knowledge of these processes had led to many valuable additions to our drug treasury. Substances which comprise the three great groups of nutritive material, such as albumin, fat, and carbohydrates, are reduced almost completely to their lower metabolic components in the body: CO_2, water, and urea. Generally speaking, substances of the fatty series are readily accessible to oxidation. The behavior of those bodies in which the nuclei have an annular grouping is more resistant; in these only the fatty lateral chains are oxidized, although under certain circumstances the benzol nucleus may also undergo combustion. The fatty acids are oxidized in the body without exception, as are likewise the oxy-fatty acids. It is otherwise with these bodies when the H atoms are replaced by halogen radicals. Oxidation then becomes more difficult, although trichloracetic and trichlorbutyric acids are partly oxidized with separation of HCl. The alcohols of the fatty series are oxidized to acids, as methyl-alcohol to formic acid. The esters of methyl-alcohol, like that substance itself,—methylamin, oxymethansulpho acid, formaldehyde,—also go over into formic acid. Ethyl-alcohol, acetone, and other derivatives of the fatty series do not yield formic

[27] J. W. Wainwright: Therapeutic Monthly, March, 1902.

acid. Aldehydes, however, are never produced within the body by oxidation from alcohol; but aldehydes may be reduced to alcohol, as chloral hydrate to trichlorethyl alcohol, butyl-chloral to trichlorbutyl-alcohol. The higher alcohols of the fatty series are not, however, always completely oxidized. Isopropyl-alcohol is changed in part to acetone, while the rest is excreted unchanged. The primary and secondary alcohols are readily oxidized in the body. More difficult is the sexivalent alcohol mannit, which appears in the urine of dogs almost unchanged. The tertiary and all halogen substituted alcohols are oxidized with great difficulty. Thus, tertiary amyl-alcohol,



trichlorbutyl-alcohol: CH_3. CHCl. CCl_2. CH_3. OH., appear for the most part combined with glycorunic acid in the urine. The dibasic acids behave in the following manner: Oxalic acid is partly eliminated by the urine, and shows a certain resistance to oxidation. Some claim that it undergoes no oxidation in the body whatever. Glycolic acid, CH_2 (OH). COOH, is oxidized in the body without the formation of oxalic acid, as is likewise glycoxylic acid, CHO. COOH. Malonic acid is transformed into oxalic acid only in minute amounts, while a small portion is eliminated unchanged in the urine. Tartronic acid and pyroracemic acid show themselves as combustible grain by grain. Tartaric acid goes in part unchanged through the organism. It is but slightly attacked by animal bodies."

Atropine decidedly increases the elimination of uric acid (Wood), but in toxic doses reduces the percentage of urea (Thompson). Drugs that tend to rapidly cause adrenal insufficiency, on the contrary, arrest the elimination of these products: evidence that they prevent the oxidation of toxics. Antipyrin thus inhibits the elimination of urea, and acetanilid does likewise in subjects sensitive to its effects.

All this evidence, in addition to the many kindred facts already adduced, seems to us to conclusively show that *the oxidizing substance is a prophylactic agency which converts certain toxics, especially products of metabolism, into benign and eliminable substances, by submitting them to an oxidation process.*

This constitutes a *continuous and physiological immunizing function.* Its inhibition explains various pathological processes—gout, for instance,—and accounts for the action of certain remedies—iodide of potassium—upon this and other diseases. The suprarenal overactivity induced by the physiological stimulant of the anterior pituitary: *i.e., thyro*-iodine, stands here as the curative agency by correspondingly enhancing oxidation. Still, the rôle of the oxidizing substance as a protective agency is far more marked when its position as a stimulant for *all functions of the organism* is borne in mind. Indeed, as such, the oxidizing substance becomes a most important constituent of antitoxin.

Interpreted in this manner it is clear that the antitoxic action of the oxidizing substance should be greatest when introduced into the system before the inroads of the disease have become too great: *i.e.,* while the several organs are still possessed of their recuperative powers. This characterizes the use of antitoxin, as is well known, in diphtheria and tetanus. Levy and Klemperer[28] refer to the researches of Dönitz, which show, "in a conclusive manner," according to these authors, "that the amount of serum necessary for curative purposes is the greater the longer the period of time that has elapsed between the intoxication and the institution of serum-therapy. Eight minutes after tetanus intoxication six times as much serum is required in order to save the animal as when the serum is injected immediately after the poison. After an hour the curative dose is twenty-four times the original dose; and so on, until finally a period is reached at which it is entirely impossible to save the animal, even with the largest amount of the most active serum." It is hardly necessary now to more than refer to the underlying cause of the gradual decline: the rapidly increasing insufficiency of the adrenal system, and a

[28] Levy and Klemperer: "Clinical Bacteriology," second edition, translated by A. A. Eshner.

corresponding deficiency of oxidizing substance in the blood. Among the organs stimulated by the oxidizing substance, or rather awakened to physiological activity by the injections, are those of the adrenal system itself; so that the adrenals *per se*, by resuming their functions, continue the beneficial effects of that injected into the blood. That this stimulation actually occurs may easily be shown.

Lobar pneumonia, a disease in which the adrenals seem to be stimulated to a much higher degree than in diphtheria, is attended, as is well known, by marked leucocytosis. If, as previously suggested, this phenomenon is the result of adrenal overactivity, it seems reasonable to conclude that when it is present the adrenal secretion must simultaneously be increased. The following lines quoted from Osler's "Practice of Medicine"[29] are significant: "There is in most cases a leucocytosis which appears early, persists, and disappears with the crisis. The leucocytes may number from 12,000 to 40,000 or 50,000 or even more, per cubic millimeter. The fall of the leucocytes is often slower than the drop in the fever, particularly when resolution is delayed. The annexed chart from J. S. Billings's paper[30] shows well the coincident drop in the fever and in the number of leucocytes. A point of considerable prognostic importance is that in malignant pneumonia the leucocytosis may be absent, and in any case the continuous absence may be regarded as an unfavorable sign. Of 50 cases shown in my clinic during the sessions of 1896-97 and 1897-98, the lowest was 10,200." Von Limbeck noted this coincidence in 1889.

It is plain that if a high degree of leucocytosis indicates a correspondingly high rate of adrenal overactivity and the fever follows the same fluctuations, the glands must also underlie the production of the latter phenomenon.

That this is the case may be shown in another way. We know that lobar pneumonia is sometimes afebrile in children and drunkards. The weakness of the adrenals of the former has been already referred to; one of the most marked results

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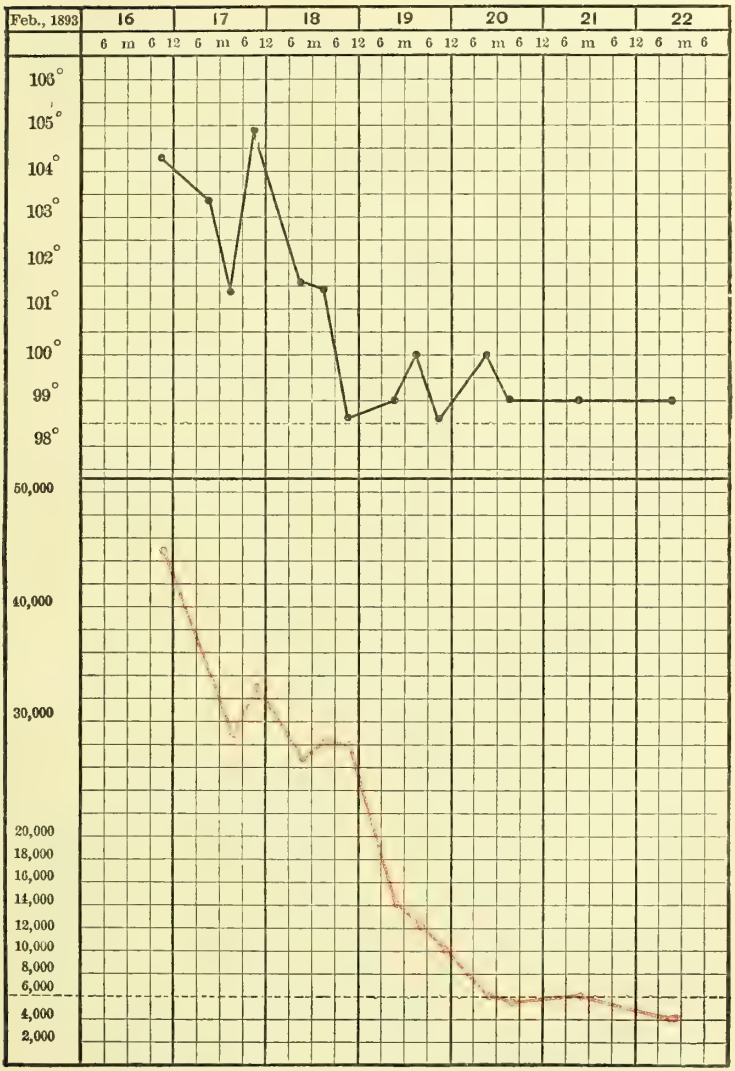
[29] Osler: Third edition; article, "Lobar Pneumonia."
[30] J. S. Billings: Johns Hopkins Hospital Bulletin, No. 43.



COINCIDENT DROP IN THE FEVER AND IN THE NUMBER OF LEUCOCYTES. (*Osler.*)

of chronic alcoholism, as will be shown later on, is adrenal insufficiency: a fact which at once accounts for the high mortality in such subjects. The violence of adrenal *protective* action in lobar pneumonia is illustrated by confirmatory signs, the blood-tinged expectoration, the full and bounding pulse, etc.—all of which suddenly cease in a few days in favorable cases when the protective process has gained the mastery through *adequate* suprarenal activity which the toxins could bring on, but not overcome.

IDENTITY OF THE PROPHYLACTIC AGENCY THROUGH WHICH TOXINS ARE ANTAGONIZED IN THE BLOOD.

After all the evidence adduced in this volume so far, we deem it unnecessary to further emphasize the fact that overactivity of the adrenals brings on corresponding overactivity of all organs—including the posterior pituitary, the general center of the nervous system, by enhancing the intensity of all oxidation processes. We still have the dominant feature of the immunizing process to ascertain, however: *i.e.*, the manner in which toxins, the direct pathogenic agencies of bacterial origin, are antagonized in the organism.

Are we dealing with a special physiological agency intended to destroy such substances? The multiplicity of pathogenic organisms suggests the existence of a correspondingly great number of varieties of toxins and the need of equally numerous kinds of counteracting agents. In other words, the question of specificity at once recurs. We have seen, however, that this feature of immunity is not generally thought to be subject to close limitations. While Levy and Klemperer[31] refer only to exceptions to the rule, Hueppe[32] says: "Antitoxins that are formed specifically in serum act *in vitro* upon poisons of a specifically different character in the same manner as upon poisons specifically similar, while the converse does not always obtain; antivenin annuls the poisonous effect of abrin, but not of diphtheria toxin, tetanus toxin, or ricin; antiabrin neutralizes the toxic effect of snake-venom, diphtheria toxin, and ricin, but not that of tetanus toxin; tetanus antitoxin is antag-

[31] Levy and Klemperer: *Loc. cit.*
[32] Hueppe: Quoted by McFarland, *loc. cit.*

onistic to snake-venom, but powerless against ricin and abrin; rabies serum is potent against snake-venom, but impotent against the diphtheria and tetanus toxins, and against ricin and abrin; streptococcus serum is potent against snake-venom, powerless against the others; cholera serum is moderately effective against snake-venom, but without effect against the others; diphtheria antitoxin is pôwerless against snake-venom, tetanus toxin, ricin, and abrin; the antitoxic sera of swine, erysipelas and typhoid are powerless against all these poisons."

Of course, these experiments are only referred to in this connection to show that it is only in the light of *prevailing views* that there is good ground for the assertion that specificity is not subject to close limitations: a statement which, given its true meaning, amounts to saying that the question of specificity cannot be elucidated with the aid of prevailing doctrines. Indeed, there is no connection between the action of one toxin upon another, on the one hand, and the action of the organism upon a given toxin introduced into the circulation, on the other, even irrespective of any of the views we have submitted. If, in addition, the fact that the experiments were performed *in vitro, i.e.*, apart from chemical influence which the constituents of living blood and cells may exert upon the toxins, is taken into consideration, it becomes clear that the evidence they afford is misleading. Indeed, the clinical side of the question affirms the contrary; as we interpret its teachings, they clearly indicate that each germ, *i.e.*, each toxin, as is the case with *any* poison, possesses its own characteristic properties as a molecular structure. True, there is considerable resemblance between the effects of various toxics, and groups of these agencies, such as those represented by "sedatives," "cerebral stimulants," "narcotics," etc., in pharmacodynamics, may be formed. But this only further emphasizes the truth of clinical teachings, since the need of dividing the many remedies represented into groups affirms the dissimilarity of effects shown by these groups. That each group is itself composed of specific agencies, each of which is endowed with its own *mode* of action, is as well known; ether and chloroform, for instance, are both anæsthetics, but they differ materially in their effects upon the organism if absolute specificity is accepted as standard. These

commonplace facts *appear* so because they are so firmly established that no one even thinks of disputing them. But this in itself embodies the deduction we wish to reach: *i.e.*, that *specificity is a factor of general toxicology* (including toxins and venoms) established on so firm a foundation that we would regard all the work submitted in this volume as fallacious did our views conflict with it. And, indeed, the fact that the one organ, the anterior pituitary, is the organism's guardian would tend to suggest an opposite deduction; but even a cursory review of the functions of the adrenal system, as we understand them, confirms the teachings of practical experience.

Indeed, since the adrenal system, to which we ascribe the primary rôle in the prophylactic processes involved, is subject to fluctuations of functional activity, and these, in turn, depend upon the virulence of the toxic and the dose of the latter, "specificity" must represent, as regards major symptoms, variations of suprarenal activity: a feature which harmonizes perfectly with the effects of the various poisons, venoms, etc., already reviewed. A given toxin under these conditions could only stimulate the adrenal system up to a certain degree, but not beyond. That this conception is not erroneous is suggested by the fact that it accounts for the antitoxin record of the horse referred to by McFarland, which reached 1400 units to the cubic centimeter, then gradually declined to 100 units. While this particular horse's adrenal system could stand stimulation perhaps above this stage, it was the only stage to which diphtheria toxins could bring it.

The specificity of toxics in general is further shown by the constancy of the effects of a given drug in a normal subject and the dissimilarity of these effects from those of another drug. Quinine, for instance, will give rise to cerebral phenomena, doubtless caused by hyperæmia and engorgement of the capillaries and—if our views are sound—of the glia-cells and fibers. This hyperæmia the bromides will never produce: simply because they are hardly able to stimulate the adrenal system beyond its normal functional activity before they lower it; and, simultaneously, the oxidation processes of the entire organism. Indeed, when the entire list of drugs is arranged in the order of their inherent potential as regards the reaction they initiate

in the adrenal system, each one is found to occupy a distinct place, as a *specific* agency. And toxins do not differ from them.

This brings us back to the identity of the process through which the pathogenic toxins are antagonized. Stimulation of the adrenal system and its normal consequence, leucocytogenesis,—which involves an increase of phagocytes and alexins in the blood to destroy bacteria,—adequately fulfilling the required bactericidal functions, to what organ can we ascribe the formation of the principle which destroys bacterial toxins?

TRYPSIN AS THE TOXIN-DESTROYING AGENT.

We have previously referred to the identity of toxins, venoms, vegetable poisons, etc., as albuminoid bodies: a fact which at once suggests that we have in trypsin a potent toxin-destroying agent. To indicate the overwhelming importance in the organism which trypsin must fulfill, if our views are sound, and to further affirm the identity of these toxins as albuminoids, the following selections from the pen of a master in physiological chemistry, Professor Armand Gautier,[33] are submitted:—

"Classification of the Immediate Derivatives of Albuminoid Substances. — We will divide into four classes the nitrogenous derivatives between protoplasmic proteids and urea, the simplest term of the nitrogenous-body series. The following four classes represent, in their actual order, the various steps of cellular disassimilation:—

"First class: Proteid derivatives of tissue albuminoids.
Peptones—toxalbumins or toxins.
Diastases and soluble ferments.
Venoms and vaccines.
Pigments.

"Second class: Amid bodies.
Complex amids.
Fatty-acid amids.
Tyrosin.
Amids containing sulphur.

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[33] Armand Gautier: "Chimie de la Cellule vivante," pp. 102 *et seq.*

"Third class: Leucomaines of animal bases.
(a) Neurin leucomaines.
(b) Creatin leucomaines.
(c) Xanthic leucomaines.
(d) Unclassified leucomaines.
Appendix: Ptomaines.

"Fourth class: Ureides.
Mono-ureides.
Di-ureides, etc.

"We do not intend to describe these substances, but simply indicate the origin of each, the principal ways in which they are split, and their rôle in the economy.

"*First Class: Albuminoid Derivatives.—(a) Peptones.*—We have seen that proteid substances when split by hydration, are converted into peptones in the intestine, and that, though much lower in molecular weight than their antecedent albuminoids, these peptones nevertheless preserve the general characters of the latter. They represent their immediate derivatives.

"As is the case with proteid substances, peptones contain five elements: carbon, hydrogen, oxygen, nitrogen, and sulphur in analogous proportions; they also tend, as do the former, to become transformed into complex amids that accompany urea and oxamids, which can undergo autoconversion, if hydration continues, into carbonate and oxalate of ammonia. By means of further hydration peptones may be split up into acid amids —leucin, glycocoll, tyrosin, etc.—and ammoniacal salts. They give the Millon and biuret reactions. They are, therefore, essentially albuminoid.

. . . . . .

"These very distinct basic properties of peptones, that are hardly perceptible in the albuminoids from which they are derived, make them the first term of the series of animal bases or leucomaines. Before I had discovered the latter substances, the basic properties of peptones were practically unperceived, or, at least, they failed to attract interest; but to-day we are aware that, besides these alkaloidal characteristics, peptones are likewise toxic in rather large doses. Toxins, venoms, diastases, secreted by microbes, white corpuscles, and certain glands,

also possess this characteristic of peptones, of being both albuminoid and basic, and, as such, belong to the family of complex leucomaines produced by animals. Peptones and toxalbumins constitute the subclass of proteid leucomaines.

"It is not only in the products of gastric and intestinal digestion that peptones are met with. Many are to be found in animal and vegetable cells, particularly in white corpuscles, the lymphatic corpuscles that migrate from vessels, in embryonic cells; in glands and in some instances (purulent foci, nervous diseases) in the blood and urine; finally, in venoms. Many microbes owe their toxicity to the peptones they secrete.

"It is very probable that the peptonization of albuminoids produced in many cells of the economy, is due to the presence in these of a certain quantity of pepsin or analogous ferments (papain, pancreatin, etc.): substances that have been observed, outside of the gastric and intestinal glands, in the lymphatics and in normal urine, for example.

"*(b) Toxalbumins: Toxins.*—Many normal tissues, treated with cold water, or, better, with an aqueous salt (7 or 8 per 1000) solution, furnish extracts which, deprived of their crystallizable bodies by dialysis, are extremely toxic: such, for instance, are the extracts of spleen and especially of liver. A dose of such an extract corresponding to 15 or 20 grammes of hepatic tissue produces, in animals, extreme lassitude with contraction of the pupil; after one to two hours they are taken with diarrhœa and die in prostration (Roger). Aqueous extract of kidney, prepared cold, causes pyrexia (Lépine). This toxicity seems to be especially due to certain soluble specific albuminoid substances, comparable to that of venoms, since, when heated to 100° C., the extracts lose the greater part of their toxicity.

"The production of albuminoid venoms by animals and plants is now an established fact. It was in 1883 that Weir Mitchell and T. Reichert observed that the venom of snakes—particularly that of the rattlesnake and of the moccasin—contained three specific albuminoid substances: a venopeptone, a venoglobulin, and a venoalbumin. The two former are alone venomous. They also observed (a feature which I had noted a year before in connection with cobra-venom) that a tempera-

ture of 100° C. perceptibly altered the action of these substances, without causing it to disappear. Wall had observed prior to my researches that, when daboïa venom is heated, it loses its convulsing power, but not its toxicity, as if only one of the active substances were altered by heat.

"Soon after these researches, N. Wolfenden obtained from the *cobra capello* venom an inert peptone, and also very toxic globulin, serin, and casein. The serin kills by inducing ascending paralysis of the cord; the globulin, the most powerful of the three former, assails the respiratory centers; the casein acts similarly, but less actively.

"It is now well known that the blood of some animals deemed inoffensive contains toxic albuminoids; such is the blood of the eel and of the murænidæ (Mosso), the blood of the water-snake (Phisalix and Bertrand), and that of the viper. Finally, certain spiders have also been found to contain toxalbumins.

"This property of the economy of thus producing toxic albuminoids is evidently pretty general as well among the larger animals as among inferior species; toxic mushrooms and microbes often manufacture toxalbumins. Christmas has shown that the poison secreted by the staphylococcus aureus is albuminoid in nature; it possesses the attributes of these bodies—it is digested by pepsin, leaving a nuclein residue, which can be precipitated with alcohol. Injected under the skin, it produces, in animals, a chronic cachexia (Gamaléia).

"Venomous albumins have also been found in ricin-seeds, in those of the yellow lupine, in the fruits of the papaw and of the jequirity; in the bark of the robinia pseudo-acacia.

"All these toxins lose a great part of their activity when heated, even though their extracts do not become coagulated.

"*(c) Diastasic Ferments.* — From the toxalbumins to the diastases there is but a step, although these substances essentially differ. The origin of the latter, however, is especially vegetable.

"Tuberculin, the active substance of the Koch bacillus cultures, is obtained by methodically precipitating these cultures by means of alcohol. It possesses all the properties of albuminoids (Millon, Adamkiewicz, and biuret reactions); phos-

photungstic acid, tannin, and sulphate of ammonium precipitate it completely.

"The active ferment of glanders, mallein, is also albuminoid in nature. Such is also the case with the diastase of epizootic pneumonia of cattle (Arloing).

. . . . . .

"Between toxic peptones, the albumotoxins of venoms, of toxic bloods and the diastasic ferments, it is difficult to establish a limit other than their origin or their more or less marked activity: 0.00008 gramme of cobra-venom suffice to kill a kilogramme of rabbit; 0.0021 gramme of viper-venom, 0.01 gramme of jequirity globulin, or 0.30 gramme of ordinary peptone are necessary to produce the same effects.

. . . . . .

"The gradation is imperceptible from inoffensive albumins to toxalbumins, or peptones; and from peptones to leucomaines. From toxalbumins to vaccines there is but one step. It is known to-day that viper-venom, and perhaps that of the cobra capello, when heated and injected into the tissues, become true vaccines which preserve animals against the action of these same venoms (Phisalix and Bertrand). But *what is remarkable* with the action of these soluble poisons, is that, as is the case with vaccines, the toxins appear to act rather as ferments by modifying slowly and deeply the general nutrition of cells, than as chemical poisons. Indeed, *their action is not immediate; it is only after a certain period of incubation that the fermentation occurs which gives rise either to immunity or to disease.*[34] This, at least, is what occurs with the toxins of heated venoms and with those of tetanus.

"The slowness of the action of these soluble poisons is nevertheless not contradictory to the theory that their action is purely chemical. Molecules possessed of mixed functions react all the more slowly the one upon the other as they are heavier and less active as conductors. This is the case with albuminoid substances."

We thus have as *main sources of intoxication, which it is the function of trypsin to counteract,* the following agencies:—

1. Toxins and diastases secreted by bacteria.

[34] The italics are our own.

2. Diastases derived from leucocytes and glandular elements.
3. Tissue toxalbumins.
4. Snake- and other venoms.
5. Vegetable toxalbumins.
6. Diastasic ferments.

At the end of the eighth chapter we offered the following deductions: 1. The cleavage processes to which trypsin submits albumins in the intestinal canal include the preliminary steps of a protective function. 2. The spleno-pancreatic internal secretion is represented by the trypsin which reaches the portal vein by way of the splenic vein, and which continues in the blood-stream the cleavage processes begun in the intestinal canal. 3. The main function of the spleno-pancreatic secretion, trypsin, in the blood-stream is to protect the organism from the effects of the toxic derivatives of albuminoid bodies.

That albuminoid poisons, including bacterial toxins, are destroyed by the spleno-pancreatic ferment—trypsin—may also be sustained by experimental data. Charrin and Levaditi[35] not only ascertained that toxins introduced into the digestive tract were modified, but that the pancreatic secretion played the preponderating rôle in this connection. Diphtheria bacilli, injected into the pancreas of animals, lost their activity, while the same quantity injected in the muscles proved toxic. Pancreatic extract itself was found to destroy micro-organisms. In the light of the views herein recorded the active pancreatic substance was the trypsin contained in the veins and ampullæ of the organ. Zaremba,[36] in a series of experiments, ascertained that toxins were greatly altered in the digestive tract, especially those of tetanus and diphtheria. To ascertain whether pancreatic ferments exercised any influence in this direction, he prepared extracts of this organ and mixed them with diphtheria toxins. The pancreas extract of young animals—pups, rabbits, etc.—was found to markedly reduce the virulence of the toxin. Human pancreas was found inactive, but suspecting that this was due to post-mortem changes in the organ, a number of hours having elapsed before the pancreases first obtained

[35] Charrin and Levaditi: Semaine Médicale, March 22, 1899.
[36] Zaremba: Archiv für Verdauungs-Krankheiten, Bd. vi, H. 4, 1900.

had been removed from the body, he succeeded in getting that of a boy four and a half years old two hours after death. This organ proved to be distinctly active against toxins, and in several instances the pancreases of very young children removed immediately after death were very active in the same way. In some, however, and in older subjects and animals, no results were obtained. We have seen that the period of splenic activity or spleno-pancreatic digestion was the only one during which trypsin was formed, as shown by the experiments of Schiff and Herzen; that Zaremba's exceptions were made up of pancreases in the passive state—*i.e.*, when only the inactive zymogens of all three ferments were present—is probable.

The results of removal of the spleen, in this connection, are also suggestive. But here it is necessary to avoid being misled by the action of injected toxics upon the adrenal system, since a sufficient dose will kill an animal irrespective of the presence or absence of its spleen. This is well illustrated in the following experiment: "Martinotto and Barbacci[37] studied the function of the spleen in infectious diseases by injecting anthrax bacilli into guinea-pigs and rabbits, in some of which the spleen had previously been extirpated. The result was the same under both conditions. There were no marked elevations of temperature, but a *progressive fall*, preceding death." Again, the protection afforded through adrenal overactivity by exciting general leucocytosis and the production of alexins,—both bactericidal agencies,—must not be overlooked, since removal of the spleen does not reduce the protective powers. Indeed, the accumulation of toxic elements in the blood that follows splenectomy tends to increase the latter and thus compensate for the missing organ's beneficial influence. Both these features are well shown in the experiments of Courmont and Duffau,[38] who found that, in rabbits splenectomized from two to twenty-five days beforehand, the staphylococcus pyogenes and the bacillus pyocyaneus caused death in a few hours, whereas normal rabbits survived longer or altogether. Yet, when attenuated cultures of the very virulent streptococcus were used, animals splenectomized a few hours

[37] Martinotto and Barbacci: Il Morgagni, Milan, Sept., Oct., 1891.
[38] Courmont and Duffau: Société de Biologie, Lancet, June 27, 1896.

or days before always resisted better than normal rabbits, and sometimes survived when the cultures used were further weakened. The splenectomized rabbits simply had their adrenals stimulated by *two* active toxic agencies, the normal rabbits only by one, and the bacteria in the former were introduced when the blood was filled with defensive bactericidal agents. The fact, however, that the weaker organisms caused death in splenectomized animals in a few hours, whereas normal rabbits survived longer or altogether, is none the less corroborative testimony, since it suggests that in the latter animals the only poisonous agents present, the toxins, had been destroyed when formed. Indeed, Courmont and Duffau found that the staphylococcus killed a splenectomized animal in ten hours, while the same dose used in normal rabbits only caused death a week later.

A predominating feature of all experiments of this kind is the evident compensative influence of adrenal origin — so marked at times as to entirely offset the loss and even to temporarily and perhaps permanently, in some instances, provide unusual immunity to *bacteria*, the source of toxins. Thus, Blumreich and Jacoby[39] observed that when bacteria of various diseases—diphtheria, cholera, etc.—were injected into splenectomized animals, these lived longer or died less often than the normal ones. They conducted experiments with toxins, but these experiments all indicate that adrenal overactivity equalized conditions whether the spleen has been removed or not. Briefly, while in some experiments there is distinct evidence of temporary vulnerability to the effects of toxalbumins,—*i.e.*, toxins,—the majority of them as strikingly illustrate an immediate compensative influence: *i.e.*, a more or less marked increase of the activity of the adrenal system, which floods the circulation with phagocytes, alexocytes, and oxidizing substance. The enlargement of the spleen in fevers is familiar to all clinicians. This may be, besides the result of mechanical engorgement of adrenal origin, an additional source of protection whereby albuminoid bodies are destroyed through the excess of trypsin produced.

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[39] Blumreich and Jacoby: Berliner klin. Wochenschrift, No. 21, 1897.

All these facts not only further emphasize the importance of the adrenal system in the organism, but they also indicate that the spleen is not the useless organ that it is thought to be by many. True, its removal is not always followed with untoward effects, but this is merely due to the fact, illustrated above, that *the adrenal overactivity caused by the accumulation in the blood of substances that would be destroyed in the liver if the spleen were present correspondingly activates all the remaining protective functions.*

Interesting in this connection is the fact that the thyroid gland is considered by many observers, including Bardeleben, as the compensative organ of the spleen. That the adrenal symptoms have invariably been ascribed to the thyroid we have seen. General enlargement of the lymphatic glands and intense congestion of the bone-marrow have also been noted: evidence that the production of leucocytes is very actively stimulated. We have curious testimony as regards the *continuousness of adrenal overactivity* in a series of experiments conducted by H. Martyn Jordan,[40] which showed that partial excision of the spleen in pups caused these to grow "somewhat faster than their untouched brother." We have studied the morbid influence of excessive adrenal activity in exophthalmic goiter, acromegaly, etc., and noted the increased functional metabolism of the erethic stages in both diseases. It seems clear that in Jordan's experiments the unusually rapid growth of the animals can be ascribed to adrenal overactivity—a fact simultaneously proving its actual existence.

That the spleen is a protective organ is also suggested by the great amount of lymphoid tissue it contains and the large number of leucocytes it contributes to the portal circulation. In this particular, however, we only regard this organ as one of several sources of supply, and merely refer to it to show that in addition to its *main function, the secretion of a ferment,* it is occupied by leucocyte-forming structures such as there are in other parts of the *digestive system,* of which the spleen is an essential member. Indeed, the description of an intestinal solitary follicle or of one of those that take part in the

[40] H. Martyn Jordan: Lancet, Jan. 22, 1898.

formation of a Peyer patch, including the central "secondary nodule" of Flemming,[41] could as well be applied to splenic lymphoid structures. These probably also subserve a dual process, such as that observed by Macallum in the intestine, judging from the fact that the splenic lymphocytes often contain iron-pigment. This suggests that in the spleen the leucocytes formed pass out into the pulp-channels and chemotactically take up the iron-pigment then carry it to the liver *via* the portal vein, just as in the intestine they are also formed in the follicle, pass out into the intestinal tract, take a similar supply, re-enter through the villi, and also proceed to the liver via the portal vein. Again, the power of the intestinal leucocytes to chemotactically take up iron-pigment demonstrates their capability of acting similarly with bacteria; the same may be said of splenic leucocytes, thus justifying Metchnikoff's view that phagocytosis is one of the spleen's weapons in defense of the economy.

All these features emphasize the identity of the spleno-pancreatic ferment as a prophylactic agency, and we now feel that we can, with confidence, submit the following conclusions:—

1. The spleno-pancreatic system, through the agency of its proteid-digesting ferment, trypsin, protects the system against diseases caused by toxic albuminoid bodies.

2. The main toxic albuminoid bodies to the effects of which the system is exposed are:—

(a) Toxins and diastases secreted by bacteria.
(b) Vegetable toxalbumins.
(c) Proteid toxalbumins. } *Toxic foods.*
(d) Peptone toxalbumins.
(e) Vegetable poisons.
(f) Venoms.

3. Trypsin is the constituent of antitoxin which splits the toxins of the diphtheria bacillus into inert bodies.

4. Trypsin is the constituent of blood-plasma which splits all toxic albuminoids into inert bodies and thereby protects the system against diseases due to their effects.

[41] We purposely omit the term "germ-center," employed by Flemming, to avoid the confusion that its use would obviously entail.

THE COMPOSITION OF ANTITOXIN.

A review of the data submitted shows that *phagocytosis* has fully merited the recognition it has received. This is due mainly to the labors of Metchnikoff, who propounded the doctrine and whose views have been sustained by the investigations of other observers. It has also proven itself unassailable by, and eminently in keeping with, the views submitted in the present volume. The mobile phagocytes in the blood-plasma and the fixed phagocytes—*i.e.*, the endothelial, hepatic-stellate, connective-tissue, bone-marrow, lymphatic, and splenic-pulp cells, etc.—unitedly constitute a protective system through which all the living structures of the organism are primarily protected. Phagocytes incorporate not only dead, but living, bacteria, and are able to destroy them. They thus prevent their pullulation and the production of toxins. The analysis has also shown:—

That *alexins*, the presence of which in the body-fluids has been shown through the labors of Hankin, Buchner, and other observers, are likewise bactericidal and constitute active prophlactic agencies has also been sustained herein. Alexins are secreted by leucocytes, and the bactericidal activity of the blood-serum corresponds with the number of leucocytes present in it. Their destructive power varies according to the microorganism present, though all are more or less weakened by them. They also act, according to Buchner, as histolytic enzymes, capable of softening or even causing dissolution of morbid histogenetic elements, abscesses, tubercles, etc.

That *trypsin*, to which we attribute the main prophylactic function,—*i.e.*, that of a proteolytic ferment capable of reducing bacterial toxins, toxalbumins, vegetable poisons, and venoms to benign products,—is, in reality, endowed with these functions, seems to us as fully sustained by the analysis to which we have submitted this question. Its specific action upon albuminoids has been experimentally demonstrated, while the identity of the above pathogenic bodies as albuminoids is as conclusively established.

That the *oxidizing substance*, to which we attribute the prophylactic function of destroying by oxidation all toxic agen-

cies susceptible to such a reaction that may either be physiologically formed in the organism or enter the blood-stream from without, is the reagent to which all such processes are due has likewise been demonstrated by its rôle in general functions: the combustion of sugars and other hydrocarbons, the elaboration of uric acid, phosphoric acid, etc.

That the *thyroid secretion,* which contains iodine in organic combination, as demonstrated by various investigators, sustains the functional activity of the anterior pituitary body and, therefore, of the entire adrenal system. Being endowed with antiseptic and stimulating attributes, owing to the presence of iodine, it may also act as such in the blood while in transit, but, as no experimental proof to this effect is available, its action upon the anterior pituitary body can alone be taken into account.

In view of all these facts it seems evident that phagocytes, alexins, trypsin, and the oxidizing substance are the four main defensive agencies with which the organism is provided to antagonize pathogenic germs, their toxins, and other organic poisons; and that they represent the active constituents of antitoxin. We can therefore conclude, for the time being, that:

Antitoxin, the antitoxic serum obtained from animals by means of injections of diphtheria toxins, is composed of the following main bodies: (1) Blood-serum, which acts as vehicle. (2) Alexins, which act as bactericidal agents. (3) Trypsin, which acts as toxin-, toxalbumin- (including vegetable poisons), and venom-reducing agent. (4) Oxidizing substance, which submits to oxidation all toxics possessed of sufficient affinity for oxygen.

A number of questions are awakened by this list, however. How do the alexins originate, and to what agency do they owe their bactericidal properties? Again, considerable evidence, clinical and experimental, has shown that the protective functions of the organism fluctuate under certain conditions. The introduction of salt solution into the blood-stream, for instance, often causes a seemingly moribund case to at once enter the stage of convalescence. This suggests that we have only studied the grosser phases of the immunizing process so far, and that our inquiry must include, if it is to be of some practical value, an analysis of the physiology of immunity, and of the intrinsic conditions that tend to antagonize the immunizing process.

CHAPTER XII.

THE INTERNAL SECRETIONS AND THE PRESERVATION OF LIFE.

Willoughby[1] refers to a case of opium poisoning in which the narcosis was so profound that the application of the strongest possible interrupted current to the soles of both feet did not excite the slightest movement even of the toes. When about a quart of salt solution had been infused by gravitation into the subcutaneous tissue of the flank, the effect was almost immediate and striking. Within twenty minutes the duskiness and coldness of the skin had given place to a natural color and warmth, and the patient had so far recovered sensibility and consciousness as to struggle violently against the mechanical and electrical stimulation employed to keep her awake.

What is the intimate nature of the process through which saline solutions are enabled to so wonderfully restore functional activity? In the course of investigations concerning the distribution of intravenously injected solutions of chloride of sodium and chlorate of sodium, Sollmann[2] found that, when they were introduced directly into the blood-stream in large quantities, the greater portion of them had disappeared in three minutes, while in one-half hour the composition of the blood was about as it was originally. A curious fact noted was that the total quantity of blood was diminished notwithstanding the injection of a large quantity of fluid. The latter left the blood-stream to enter the "tissues," then passed out in the urine. The itinerary of the fluid and salts up to their final excretion was completed in about half an hour, and the molecular concentration of the plasma showed no marked change.

In the light of our views, the "tissues," *i.e.*, the protoplasmic cellular elements of which they are composed, are evidently not the structures *primarily* influenced by the presence

[1] Willoughby: Lancet, May 10, 1902.

[2] Sollmann: Archiv für experimentelle Pathologie und Pharmakologie, Bd. xlvi, H. 1 und 2, 1901.

of the solution in the blood, but, instead, the *functional* constituents of the tissues, *i.e.*, myosinogen, myelin, etc. Again, the rapid disappearance of the alkaline solution from the blood-stream does not point to tissue absorption, but to escape into the lymphatic spaces and circulation, the aggregate area of which is over twice that of the blood-system.

The introduction of the lymphatic system as a factor of the problem before us, at once recalls the all-important protective rôle that leucocytes,—as phagocytes, alexocytes, etc.,—reviewed in the last chapter, play in the economy; it also recalls the evident connection between leucocytosis, or rather leucocytogenesis, with all morbid processes. May we not have in these white blood-corpuscles—so little concerning which, as regards their intrinsic biochemical function, is known—the main factor in the striking resuscitations which the use of saline solution procures? These amœboid cells must doubtless be hampered in their movements (for they are not merely dragged along as are the red corpuscles) as soon as the specific gravity of the serum is raised; their pseudopodia cannot but lose the freedom which adequate alkalinity of the fluid in which they live had previously insured.

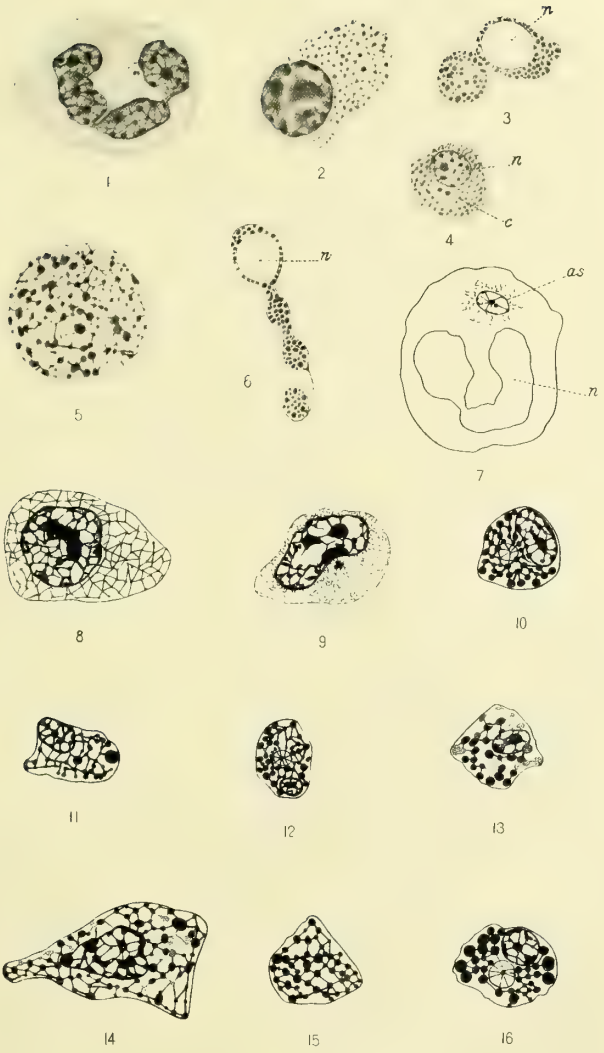
Indeed, the closer is the intimate nature of the leucocyte examined, the more does one become impressed with the thought that this cell must be endowed with functions greatly exceeding in importance any as yet ascribed to it.

THE LEUCOCYTE IN ITS RELATIONS TO LIFE AND ORGANIC FUNCTIONS.

Before inquiring into the physiological functions of each of the various varieties of white corpuscles or leucocytes, we have thought it advisable to study the cell as a unit, and particularly the functional attributes of its main component structures: (1) the nuclear and cellular reticulum or mitoma; (2) the granules.

THE MITOMA.—Alluding to basophile leucocytes, Howell[3] states that the nucleus "is divided into lobes that are either entirely separated or are connected by fine protoplasmic threads."

[3] Howell: *Loc. cit.*



LEUCOCYTES: THEIR MITOMA AND MICROSOMES. *[Gulland.]*

[*Journal of Physiology.*]

This is well illustrated in the annexed plate from a valuable study of the subject by G. L. Gulland,[4] by Fig. 1, a hyaline leucocyte from a newt's blood. These cells are undeveloped and their protoplasm does not as yet show "threads." But their nucleus is clearly supplied with them even at this early stage—a feature which suggests that the nucleus is an autonomous structure. This is further sustained by the presence, in the perinuclear portion of the cell, of a small body, the astrophere, shown in Fig. 7, another undeveloped, or "hyaline," cell. This astrophere is likewise present in fully developed leucocytes, as may be seen in Figs. 10, 12, and 16. Each cell may, therefore, be said to contain two functional centers, each supplied with its net-work of fibers or threads.

Heidenhain is stated by Gulland to have found that "the granules are arranged radially to the astrophere, with the smallest granules next the sphere, the largest at the periphery." This is exemplified with especial clearness in Figs. 10 and 16, and if the threads, or fibers, are traced from the center of the astrophere, the gradual increase in size of granules as the periphery of the cell is approached is clearly indicated. Heidenhain also concluded, a feature fully confirmed by Gulland, that "there are never any granules within the astrophere itself." It thus becomes evident that while the nucleus is an autonomous structure, the same may be said of the astrophere. In other words, a leucocyte seems to be supplied with two individual, though doubtless correlated, functional systems: (1) the nucleus *per se*, which contains a net-work of fibrils and granules; (2) the astrophere, which represents the center of the cellular net-work of granule-laden fibrils.

As may be seen in the numerous cells represented in Gulland's plate, which cells have been drawn by him with the utmost care and fidelity to microscopical appearances, the fibers in the nucleus divide the latter into several irregular areas, while the radiating net-work of which the astrophere is the center forms relatively regular spaces. The fibers in both structures run to their external boundaries, however, precisely as if they were attached to the external limiting membranes of

[4] G. L. Gulland: Journal of Physiology, vol. xix, 1896.

each. And yet the nucleus alone seems to be supplied with such a membrane, while the surface of the cell is not. Indeed, a prominent feature of these cells is the fact that their protoplasmic exterior is absolutely bare.

After a study of the characteristics of the granules, Gulland writes: "The granules of leucocytes are therefore *not* products of the metabolic activity of the cell imbedded in a structureless protoplasm, as was hitherto supposed, but represent an altered condition of the microsomes [the granules]. They always form part of the cytomitoma [the net-work of fibers] and are therefore *plasmatic*, and not paraplastic. They are probably concerned with amœboid movement, and they and the rest of the mitoma are more visible the more active the cell." Granules, as the plate distinctly shows, are plentiful within the nucleus, and in the cellular substance likewise; indeed, in the latter they are crowded around the centrosphere, the deepest portion of the cell.

If the granules are plasmatic, *i.e.*, formed by substances derived from the plasma, how does the latter reach the minute areas in which the granules are formed? Channels seem to us absolutely necessary for the passage of the blood-plasma, its alkaline phosphates, and other plasmatic salts from which the granules are formed.

The prevailing view that the threads (mitoma) are concerned with the amœboid movements of leucocytes, as also inferred by Gulland, is by no means, it seems to us, incompatible with the possibility of their being plasma-channels, or efferent canaliculi. Indeed, their elasticity does not eliminate the possibility of their being tubular, while their extension and retraction may, as in the sweat-glands, afford the mechanical elements of an expulsive process. "It is certainly interesting to note that, the more active the cells of this series become," writes Gulland, referring to the acidophile (phagocytic) leucocytes, "the more visible become their mitoma and the microsomes which form part of it. The lymphocytes in which no mitoma can be seen are practically non-amœboid. The hyaline cells in which it is not very evident move but sluggishly. The oxyphile cells, with a well-marked mitoma and microsomes, move more rapidly, and the eosinophile cells, whose mitoma

and microsomes are the most visible of all, move most rapidly." Again, he says: "It is certain that the length of thread lying between the microsomes varies immensely in different parts of the cell, and the short threads are usually the more deeply stained; so that it looks as though they were *contracted* and therefore *thickened.* On the other hand, the microsomes at the periphery are, generally speaking, the largest, and there can be no doubt that it is the circumference of the cell which moves most and moves farthest." As regards the basophile leucocytes, he states that, "as far as one can judge from fixed specimens, the larger basophile cells seem to have more power of movement than the smaller ones"—a feature easily accounted for, since they are not bactericidal, as are the acidophile leucocytes. It seems evident, however, that in both acidophile and basophile cells the fibers take part in the mechanism through which they travel in the plasma, while contraction, thickening, etc., *i.e.*, the elements of a suction or expulsion process, are present to suggest the identity of the mechanism to which they owe their powers of locomotion.

Basophile leucocytes are not phagocytic; they do not, therefore, ingest foreign substances as do the latter, *i.e.*, by inglobing them. They must, therefore, be provided with a different mechanism for this purpose. If, in accord with our view the mitoma represents a system of centrifugal canaliculi, it cannot serve for this purpose. Indeed, the external agencies penetrate the cell to the nucleus itself. Thus W. R. Stokes and A. Wegefarth,[5] alluding to the researches of Bail,[6] say: "After injecting virulent staphylococci into the pleural cavity of rabbits he found that the leucocytes underwent a characteristic change. They formed round, empty bodies, containing several vacuoles in the *nucleus.*"

How did the virulent staphylococci reach the nucleus's vacuoles? Metchnikoff's plate (opposite page 628 in this volume) will assist us in elucidating this question. It not only forcibly illustrates what this distinguished zoologist sought to show, but likewise, it seems to us, a mechanism of ingestion,

[5] W. R. Stokes and A. Wegefarth: Bulletin of Johns Hopkins Hospital, Dec., 1897.

[6] Bail: Berliner klin. Wochenschrift, Oct. 11, 1897.

differing somewhat from the recognized "ingulfing" or "inglobing" process through which phagocytes take up germs, small particles, etc. An example of this mode of appropriating various plasmatic or foreign substances is illustrated in Fig. 5, which shows bacteria penetrating, from various directions, *into* the cell-wall, while Fig. 16 shows the bacteria *within* the perinuclear vacuole. As all the cells in Metchnikoff's plate are phagocytes, the mechanism of ingestion to which we refer is not only that of basophiles, but is obviously a feature of all leucocytes.

We must emphasize the fact that we say "perinuclear" vacuole, and not "nuclear" vacuole, for, if this and the other germ-laden cells just referred to are carefully examined, it will become evident that the bacteria lie in a pocket contiguous to, but not forming part of, the nucleus itself. We would not say, therefore, with Bail, "vacuoles *in* the nucleus," but vacuoles *around* the nucleus. Indeed, Gulland refers to Heidenhain as considering that "the nucleus lies free in the interfilar spaces, and is not organically connected with the cell-substance." This is quite in accord with our view, and it seems to us that it represents the cavity into which bodies ingested by leucocytes normally arrive, though smaller vacuoles are likewise present in the cytoplasm.

The actual presence of this perineuclear vacuole from which canaliculi would start appears to us indicated in several of the figures in the annexed Gulland's plate. Fig. 8, for instance, stained with iron-hæmatoxylin, shows that the nucleus is surrounded by an irregular limiting material of some kind; but if we compare the outline of this limiting substance with that of all the succeeding cells, an interesting feature asserts itself, viz.: its thickness is extremely variable. Although 12 may be said to be moderately regular, the others, in the following sequence: 11, 10, 13, 8, 9, and 14, are increasingly irregular. If now this irregularity itself is scrutinized, a significant fact is revealed: *i.e.*, the bulges, or projections, in the limiting structure are all at the expense of the nucleus. In Fig. 9, for instance, just above a clover-like figure near the center of the cell (probably the astrophere), the marked bulging shows every evidence of having been formed by a substance which had com-

pressed the nuclear substance inwardly. The stages of this compression are exemplified in Metchnikoff's plate, by Figs. 16 and 15, successively. In the former a single mass of liquid and germs is seen to have indented the center of the nucleus on one side, while in the second figure three cavities are shown which have distorted it. (The nucleus is indicated by an *n.*) In *both*, however, the compression has exceeded the normal boundaries of the limiting structure, and centrifugal bulging has occurred at the expense of the pericellular protoplasm or cytoplasm. So marked has this become in Fig. 14 that the nucleus is not discernible.

The identity of the mitoma as a system of canaliculi seems to us shown in another way. We have found that the axis-cylinders of nerves, neuroglia fibrils, etc., contained blood-plasma. Such being the case, if the fibers or "threads" in leucocytes are likewise plasma channels, they must stain, as do the former, when treated to various dyes. We have seen (pages 541 to 543) that methylene-blue, dissolved in salt solution and injected into the vessels of a living animal, colored the axis-cylinders blue, according to Ehrlich, and that this investigator defined the conditions of nerve-structure essential to the methylene-blue reaction as "oxygen saturation and alkalinity" —the very attributes of blood-plasma. Referring to the various stains used by him, Gulland says: "In examining the basophile cells I used almost entirely various methylene-blue solutions," and, later on: "The basophile cells of the dog's intestinal villi, when fixed with absolute alcohol and stained with alcoholic methylene-blue, give exactly the same results, as to mitoma and granules, as other basophiles." Evidently, as regards the methylene-blue stain, nerve-fibrils and mitoma (our canaliculi) are similar. Again, in addition to the plate we reproduce, Gulland presents two colored plates in which the characteristic affinity of each cell for stains appears; the six basophile leucocytes stained with methylene-blue (normal) distinctly show that structures which stain most deeply is the chromatic, *i.e.*, the nuclear mitoma; then, more faintly, the cellular mitoma. It seems clear that, as regards methylene-blue stain at least, the conditions are similar to those of nerves as far as the mitoma—or canaliculi—are concerned.

The same correspondence exists between nerve-fibrils and the mitoma when hæmatoxylin is used. We have seen (page 536) that, according to McCarthy, the rods that project radially from the axis-cylinder "stain with carmine and hæmatoxylin, which do not stain the myelin." The fact that the axis-cylinder takes hæmatoxylin hardly needs to be emphasized, its use in histological laboratories when nervous structures are studied being second only to picrocarmine for general staining. A beautiful example of hæmatoxylin-stained human cerebrospinal and sciatic nerves is to be found in Clarkson's "Histology," page 204, for instance. All the eosinophile leucocytes shown in the annexed plate, in which the nuclear and the perinuclear granules and mitoma are so clearly defined, were stained with Heidenhain's iron-hæmatoxylin, which only differs from the usual solution in that it colors the cellular elements that take it a dark gray or black. This also shows that it is not only with the mitoma of basophile leucocytes that the staining characteristics of nerve-fibrils—*i.e.*, plasma-containing channels—coincide, but also with that of eosinophile cells. Even Apáthy's fibrils are recalled by the effects of corresponding stains, for Senn writes,[7] referring to the minute anatomy of the leucocyte: "The reticulated structure is well shown by staining with chloride of gold, which stains the protoplasmic *strings*, but not the interstitial substance." It seems to us quite evident, therefore, that *the mitoma, i.e., the intracellular and intranuclear networks of fibers in mature leucocytes, are canaliculi for blood-plasma and for the substances contained in this fluid.*

Functional Mechanism of the Leucocyte.—We have expressed the view that the nuclear canaliculi open into a vacuole which surrounds the nucleus (see Fig. 14 in Gulland's plate) and that the outer wall of this vacuole acts as terminal for some of the canaliculi of the cell-substance. Although, as suggested by Fig. 11, the canalicular orifices that open into the vacuole from both directions may correspond (the nuclear orifices being in that case opposite the cellular openings), such is by no means always the case. Indeed, in Fig. 16, for example, but two or three of the external canaliculi seem to be con-

[7] Senn: "Principles of Surgery," third edition, 1901.

nected with the vacuole, while this cavity serves as terminal for all the *intra*nuclear channels—if such they are.

Is the connection between this vacuole and the exterior of the cell direct or indirect: *i.e.*, through separate channels leading directly to the exterior or to those connected with the astrophere's system? That the communication is independent of the latter is emphasized by the presence of granules in the path of all canaliculi, as shown in Gulland's plate. A continuous function depending upon an inflow of plasma would obviously be in constant danger of arrest were the granular channels centripetal pathways. Again, in all leucocytes, acidophiles as well as basophiles, the nucleus stains in the same manner, the granules alone, as we have seen, showing variations in this particular. The same may be said of the reticulum, for we have seen, by the staining reactions, that the compounds composing the granules are bathed in oxidizing substance. This uniformity of nuclear and cellular fluids in the canaliculi suggests the presence of a common mechanism—one, indeed, which must serve to *eliminate* its contents, judging from the fact already mentioned, that the size of the intracellular granules increases in size outwardly, the largest granules being at or near the surface. A common centrifugal canalicular system again suggests the presence of a system common to all leucocytes, whether phagocytic or not, for the introduction (not necessarily of particles or other discernible agencies) of more or less liquid or viscid bodies required by the cell for its own nutrition, or connected with its own physiological functions: *i.e.*, the elaboration of granules. The canaliculi serving only for the centrifugal elimination of the latter, the centripetal paths must penetrate to the vacuoles *between* the canaliculi, or "threads," as already explained, and as shown in Metchnikoff's plate, Fig. 5. We are evidently not dealing here with mere inclusion or pseudopodial flowing around the germs, for the latter may be seen to penetrate the cell between the granules, and, judging from Figs. 13, 14, 15, and 16, directly into the perinuclear vacuole itself.

Is the cell supplied with *centripetal* canaliculi *in addition* to the centrifugal system which we believe to be represented by the reticulum? The fact that micro-organisms can pene-

trate directly *into* the vacuole between the external layer of granules is not alone to suggest that such is the case, but the manner in which the leucocyte takes up stains likewise does so. As can readily be seen, the absorption of the dye by the cell occurs without involving any alteration of its shape which can at all be associated with the process. That the absorption cannot occur through the visible canaliculi, *i.e.*, those that take stain because they constantly contain fluid, is rendered very probable by the presence of the granules, which must entirely close their external orifices. It must occur, therefore, through paths presenting some analogy to the pores of certain sponges, which allow the surrounding water to pass into the interior of the sponge, so long as it does not carry any harmful products along with it (Metchnikoff). And yet the fact that such a system of channels does not exist is shown by the promiscuous directions taken by bacteria in penetrating into the cell. Indeed, their bodies are not directed axially toward the perinuclear vacuole; they seem, once within the external layer of granules, to point in almost any direction. We are brought back, therefore, to the soft, yielding, protoplasmic cell-substance of the amœba, which will allow liquids to easily transude through it, and the more dense materials to cleave their path into it and down to the vacuole, without leaving a wound behind them. "On introducing pigeon leucocytes filled with anthrax bacilli (to which the pigeon is very refractory) into bouillon," says Metchnikoff, "bacilli grow, *pierce* the protoplasm of the cells, and form well-developed filaments, showing definitely that the bacilli were inglobed in a living condition." We might say "ingest," however, for the perinuclear vacuole asserts its identity as a digestive organ—the familiar digestive vacuole—in several ways: *i.e.*, as a cavity in which all the materials that supply the cell with functional energy,—*i.e.*, with life,—are drawn.

Metchnikoff,[8] referring to the intracellular digestion to which amœbæ submit the materials they ingulf, writes as follows: "A closer observation of the group of protozoa compels us to the conviction that this digestive function must play an

[8] Metchnikoff: "Lectures on the Comparative Pathology of Inflammation," translated by F. A. and E. H. Starling, pp. 18 *et seq.*, 1891.

important rôle in the mutual relations of these lowly organisms. Many rhizopoda and infusoria live in media swarming with other unicellular organisms, including bacteria. The latter, which multiply very rapidly, serve as food to many of the protozoa. Thus, various amœbæ devour bacilli, which undergo certain definite changes in the interior of the protoplasm. Without altering their shape, the bacilli acquire the power of taking up solutions of vesuvine, which does not stain these microbes when living in their material conditions. Since precisely similar changes are also observed in the interior of vorticellæ and infusoria, which live on bacteria, it is evident that they are due to a digestive influence exerted by the contents of the protozoa." This conclusion is in harmony with the observation of B. Hofer[9] on digestion in amœbæ. This investigator has shown that "the more the food is altered in the interior of these rhizopods, the more easily does it stain with aniline dyes." When we consider that aniline dyes include methylene-blue, we have evidence, in view of Ehrlich's observation that the "conditions essential to the methylene-blue reaction" are "oxygen saturation and alkalinity" that the prototype of amœba, the leucocyte, must owe its nuclear functional activity to the plasma as exogenous reagent.

Metchnikoff further says: "We may often see flagellated monads taking up filaments of leptothrix several times as long as themselves, and finally inclose them in their digestive vacuoles." The process of ingestion is beautifully shown in the plate opposite page 628, in Figs. 19 and 20, the organisms here being spirilla of Asiatic cholera. "It is sometimes possible to follow all the changes undergone by the bacteria within an infusorium," continues the same investigator, "as is the case of the digestion by stentor of the sulpho-bacterium thiocystis, observed by le Dantec."[10] . . . "It is evident that the digestive function of the protoplasm of the protozoa must hinder the invasion of these animals by the lower organisms, and it is only in certain special cases that the latter can live as parasites within the rhizopoda and infusoria."

The true identity of the perinuclear vacuole seems fur-

[9] B. Hofer: Jenaische Zeitschrift, vol. xxiv, 1889.

[10] Le Dantec: "Recherches sur la digestion intracellulaire," Lille, 1891.

ther emphasized by the following lines, also quoted from Metchnikoff's text, that is to say, as interpreted by his translators: "The sponges are of such undifferentiated organization that they were long considered to be colonies of protozoa, consisting like the protospongia, of separate flagellated and amœboid individuals. Later on, it was however ascertained that they bore a certain relationship to the polyps and their allies (cœlenterata)." . . . "There are a few species, such as the siphonochalina coriacea, whose mesodermic cells alone inclose all foreign bodies; so that the cylindrical cells of the endoderm merely serve to keep up the continuous passage of the fluid through the sponge. The *phagocytes* of both layers have the power of rejecting insoluble matters, which collect in the larger efferent canals." . . . "We are, however, chiefly concerned here with the fact that the mesodermic phagocytes are able to *digest* the substances as well as to inglobe them, and to *reject* the insoluble residue."

The nature of the digestive process has, however, remained obscure. "The bacilli which have been inglobed by leucocytes," continues Metchnikoff, "are much more rapidly digested in the case of mammals that are either naturally refractory, as the dog and fowl, or have been rendered artificially immune against anthrax by vaccination, as the rabbit. This fact is shown by the researches of Hess, as well as my own. It is easy to follow the digestion of many other microbes within the leucocytes. Vacuoles are often seen to form around the bacteria that have been swallowed, just as we have noticed in the digestion of nutrient material by the protoplasm of the protozoa and the myxomycetes. I have been able to observe the changes undergone by the spirilla of recurrent fever in the leucocytes of monkeys, as well as those undergone by the vibrio septicæmiæ in the leucocytes of immunized guinea-pigs, and those by erysipelas streptococci in the leucocytes of man, etc. We are at present ignorant of the precise manner in which this digestive and destructive action is accomplished, and do not even know whether the substance which kills the microbes is a ferment or not."

Before submitting this question to analysis the manner in which the products of digestion, both the nutritional ele-

ments and the excrementitious products, are disposed of must be ascertained.

In the sponge the materials rejected by the phagocytes "and which collect in the larger efferent canals," says Metchnikoff, are eliminated "through large apertures of crater-like shape, the walls of which, according to some authors, are furnished with muscular fibers." What have we in the leucocytes to fulfill this function: *i.e.*, to represent what in the higher forms constitutes the intestinal canal? It seems to us that this is particularly well shown in several of the figures in Gulland's illustration. In Fig. 10, for instance, a few "fibers" —our canaliculi—may be seen to project from the inner aspect of the line which to us represents the practically empty side of the vacuole. The same arrangement is clearly to be seen in Figs. 11, 12, 13, and 16.

If all the foregoing features are considered collectively, they seem to us to suggest that:—

1. Leucocytes can ingest solid, semisolid, and liquid bodies through their cell-substance in two ways: (1) by projecting pseudopodia which infold or inglobe them; (2) by absorbing them without projecting pseudopodia.

2. Solids and semisolids are mainly ingested by infolding, and semisolids and liquids by absorption; but all substances, with what plasma accompanies them, are collected in a vacuole that surrounds the nucleus and in which the latter lies free; and, at times, in the smaller vacuoles in the cytoplasm.

3. What physiologically useful bodies are formed in the cell are mainly elaborated in the nuclear canaliculi and the perinuclear vacuole, and are collected in the form of granules in the canaliculi.

4. All the functions of the cell are probably governed by the astrophere.

The Granules as Secretory Products.—Gulland refers to granules or microsomes in the following words: "Ehrlich regarded the seven varieties of granules which he described as being all formed by the cells, and as being either reserve material or products for excretion. Hankin [1892-93] took the view that the acidophile granules were secretory products, containing 'alexins,' and destined to be secreted into the blood or lymph. Kanthack, Hardy, and Keng have taken much the

same view of these special granules. Sherrington has thrown doubt upon it, and Metchnikoff disputes it and regards the eosinophile granules as reserve material." As viewed from our standpoint, the granules simultaneously represent reserve material *and* products of excretion. These processes are not the only ones, however, with which leucocytes are concerned.

Bail, to whose investigations we have already referred, is also stated by Stokes and Wegefarth[11] to have observed that, after the vacuole "in the nucleus" had formed, "the granules generally disappeared." Furthermore, he noted that upon destroying the staphylococci by adding ether, and diluting the centrifugalized sediment, the granules showed a dancing motion, and were seen to *leave the periphery of the cell* and enter the surrounding medium. Evidently at least *some* of the granules must have been dropped or ejected by the leucocytes, and their canaliculi thus freed of the impediment their presence constituted.

This is sustained by a closer examination of the question, —the purpose of Stokes and Wegefarth's paper, who used in their researches blood taken from about five hundred persons. The granules, when observed by them with the aid of artificial light, "resembled those of the eosinophilic or neutrophilic leucocyte." Kept at the temperature of the room, the latter showed no activity, but exposure for an hour to a temperature of 35° C. caused them to become active. The following lines are quoted from their article: "At times the granular leucocytes become actively amœboid, and the granules *within* the neutrophile exhibit a characteristic activity which might be compared to the swarming of bees around a hive. The number of fine granules free in the plasma is perceptibly increased. The eosinophilic granulations also show a less vigorous tremulous motion, and both varieties follow the changes in the direction of the pseudopodia, the protoplasm being thrown out first, and the granules following. The characteristic dancing motion of the granules in the neutrophilic leucocyte can be brought out very plainly by simply mixing the drop of blood with an equal amount of distilled water containing 1 per cent.

[11] Stokes and Wegefarth: *Loc. cit.*

of alcohol. The granules become very active and present a characteristic picture." . . .

"Can these granules be actually seen to leave the leucocyte? It is certainly not easy to be sure, even after continuous observation for an hour or more, that one has actually seen one of these granules leave an amœboid leucocyte. We think, however, that we have observed this phenomenon upon several occasions, both in fresh specimens of blood exposed to 35° C. and in blood to which 1 per cent. of alcohol has been added." Farther on in their text they say: "Many fine granules can be seen in the clear plasma and around the neutrophile, and it would seem that occasionally a granule leaves the active leucocyte and becomes free in the surrounding fluid."

Bail's observation, however, that the granules actually leave the periphery of the cell has been sustained by other observers. Gulland refers to this feature of the problem in the following words: "It has often been remarked that the large cells show a great tendency to leave their granules behind them; thus, one might come on a group of granules while the nearest cell was far away. Ballowitz was, I think, the first to declare that all or most of these groups of granules were attached to the cell by fine protoplasmic bridges. It is not always easy to show this." Gulland then says, referring to a figure in one of his plates (not shown in that reproduced herein), in which the granules are evidently disunited from the cell: "In the cell shown in Fig. 31, which was so isolated that there could be no doubt that all the granules represented belonged to it, no trace could be made out of threads extending from granule to granule. They were probably stretched too much to allow them to be visible."

The absolute separation of the granules from the cell witnessed by Bail finds its complementary confirmation in the observation of E. B. Sangree,[12] who, after patient watching,—sometimes several hours at a time,—states that he saw "three granules escape from an eosinophile cell, and wander away until lost under rouleaux of red corpuscles, after having reached a distance of some six diameters from the parent-cell." . . .

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[12] E. B. Sangree: Philadelphia Medical Journal, March 12, 1898.

"While inside the cell," says this pathologist, "these granules had participated in the constant, though rather sedate, movements of the granule mass,—but owing, doubtless, to the difference in specific gravity of the containing medium,—instantly upon emerging from the parent-cell they underwent the wildest possible gyrations. The first to come out were two attached pole to pole, and these rolled frantically over each other, pushed this way and pulled that, all the time oscillating widely and rapidly, yet constantly and definitely traveling farther and farther from the cell, until finally lost to view. The single granule behaved in an exactly similar way. I noticed, too, that before becoming lost to view the motion of these granules had become considerably less marked and approximated more that ordinarily seen in these bodies." If these facts are considered as a normal sequence to the evidence adduced that the cellular net-work of fibers represents the secretory system of the leucocyte, it seems permissible to conclude that:—

The granules in leucocytes are the products of an intracellular metabolic process and represent a true secretion.

The Physiological Chemistry of Leucocytes. — A feature which clearly points to the autonomy of the nucleus and of the net-work of canaliculi in all leucocytes is the uniformity with which they all stain with similar dyes. The nuclear canaliculi and granules and the canaliculi of the cell-substance all take the aniline dyes, methylene-blue and methyl-green, for example: evidence that in *all* leucocytes the structures mentioned must find in the oxidizing substance a source of energy as do other organs. Beginning with the nucleus, with what chemical body contained in this part of the cell could the oxidizing substance initiate and sustain a reaction? It is, of course, not the composition of the nuclear *granules* that this question involves, but that of what might be termed the nuclear ground-substance. Foster refers to this substance in the following words: "There is present, in somewhat considerable quantity, a substance of a peculiar nature, which, since it is confined to the nuclei of the corpuscles, and further seems to be present in all nuclei, has been called *nuclein*. This nuclein, which though a complex nitrogenous body is very different in composition and nature from proteids, is remarkable, on the one hand, for being

a very stable, inert body, and, on the other, for containing a large quantity (according to some observers, *nearly 10 per cent.*) of *phosphorus*, which appears to enter more closely into the structure of the molecule than it does in the case of proteids." We evidently have, in the nuclein of the nuclear ground-substance, a body which, as does lecithin in the myelin of nerves, myosinogen in muscles, etc., enters into active combination with the oxidizing substance, and the resulting reaction must necessarily yield functional energy, as elsewhere in the organism.

The character of the reaction which the simultaneous presence of nuclein and the oxidizing substance within the precincts of the nucleus sustain is clearly suggested by the kind of dyes taken by the canaliculi (both of the nucleus and of the cell-substance) and the perinuclear vacuole. E. T. Williams,[13] in a study of the chemical properties of leucocytes, refers to this feature of the problem in the following words: "The nuclei of all three classes stain best with alkaline dyes, as methylene-blue, methyl-green, or dahlia. They are, therefore, acid." Farther on, he says: "We have seen that all nuclei are acid. They owe this property, without doubt, to the nuclein which they contain. Nuclein is acid. When boiled *with alkalies* it yields phosphoric acid. Phosphoric acid, it may be remarked, is the only mineral acid which does not coagulate albumin. It is the presence of this acid undoubtedly which makes nuclein acid. According to the experiments of Kossel, quoted by Vaughan and Novy,[14] nuclein, when boiled with acids, yields certain organic, albuminoid bases, as adenin, sarcin, xanthin, spermin, and others." . . . "We must conceive, therefore, of nuclein as some sort of a phospho-albumin whose composition has not been precisely determined." The source of the various chemical bodies involved in these processes is shown in the following lines of Professor Foster's: "The ash of the white corpuscles is characterized by containing a relatively large quantity of potassium and of phosphates, and by being relatively poor in chlorides and in sodium. But, in this respect,

[13] E. T. Williams: Boston Medical and Surgical Journal, Sept. 5, 1901.
[14] Vaughan and Novy: "Ptomaines and Leucomaines," 1891.

the corpuscle is merely an example of what seems to be a general rule (to which, however, there may be exceptions) that, while the elements of the tissues themselves are rich in potassium and phosphates, the blood-plasma on which they live abounds in chlorides and sodium salts."

The chemical process involved may easily be traced with the foregoing factors as main elements: The blood-plasma (if the views already submitted are sound) evidently reaches the nucleus through the intracanalicular substance of the cell-body; this is shown by the fact that this substance likewise—though to a less-marked degree—stains with methylene-blue. Under ordinary circumstances, according to microscopical evidence, the perinuclear vacuole is practically collapsed: *i.e.*, its nuclear wall is more or less close to that of the cell-body. This is well shown in Gulland's plate, by Figs. 10 and 12. The nucleus thus bathes in blood-plasma, and its canaliculi become filled with the latter along with the vacuole. The nuclein of the nucleus under these circumstances itself bathes in the plasma, being thus exposed to the action of the latter's oxidizing substance.

Still, this suggests the presence of a stream of plasma flowing through the nucleus itself, with the canaliculi as emunctories. The contraction and retraction of the canaliculi—or reticulum—to which Gulland and others refer represent the only mechanical device in the cell by means of which the vacuole can be drained.

These minute vessels probably serve as continuous channels for the stream of plasma, which contains, besides the oxidizing substance, the alkaline salts necessary to the intracellular processes. The plasma's oxidizing substance and the nuclein's phosphorus, thus brought into contact, liberate considerable heat, and the alkaline salts in the plasma then take part in the reaction to which Williams refers, and which involves, we have seen, the formation of phosphoric acid and other agencies to which we will presently allude.

We must not lose sight of the fact, however, that nuclein is derived from nucleo-proteids, and that during the oxidation process waste-products are formed: we have in the "adenin, sarcin, xanthin, spermin, etc.," to which Williams refers, a

series of catabolic products. This awakens an important pathological feature. We have seen that, when nucleo-proteids undergo cleavage in the organism, the process involved must be brought to a finish: *i.e.*, to the stage of phosphoric-acid formation. The penalty, if completion does not attend the series of reactions, is the presence, in the blood-stream, of the above-mentioned purin bases, which are now considered, we have seen, as the source of the so-called "gouty diathesis." Slight insufficiency of the adrenal system, therefore, by reducing the proportion of oxidizing substance in the blood, must inhibit the intracellular reactions that we have just outlined, thus giving rise to this disorder. Or the injudicious use of rich foods, by surcharging the proportion of nucleo-proteids taken up by the cells, may lead to the same result though the normal proportion of oxidizing substance be present in the plasma.

Another phenomenon which appears to us elucidated by the presence of the oxidizing substance of the plasma is the manner in which worn-out leucocytes are destroyed. As frequently observed by histologists, each of the varieties may be seen at a given time to become "oxyphile," or oxygen-loving, and to undergo disintegration. Even the eosinophile leucocytes, which, according to Metchnikoff,[15] are unable "to inglobe foreign bodies, and therefore cannot act as phagocytes," are destroyed by oxidation. The affinity of these cells for acid dyes might account for their oxidation, however, and suggest a limit; but such a limit does not exist, for basophile cells also yield to the same agency. Indeed, Gulland, referring to a figure in his colored plate which gives a vivid illustration of a cell undergoing disintegration, describes it as follows: "Degenerated basophile cell from the mesentery of newt. Methylene-blue." In other words, an eosinophile is always acidophile, while a basophile is only acidophile when it is dead or about to die. We have seen that methylene-blue stains oxygen-laden media; hence, the oxidizing substance is evidently the active factor in the destructive process.

It seems to us that we can conclude from the above data regarding the physiological chemistry of leucocytes, or white blood-corpuscles, that:—

[15] Metchnikoff: *Loc. cit.*, p. 115.

1. The granules which constitute the secretion of all varieties of leucocytes are the products of a continuous reaction in the nucleus, in which the nuclein of its nucleus, the materials ingested by the cell, and the plasmatic oxidizing substance and alkaline salts take part.

2. When a leucocyte becomes functionally incompetent it is destroyed by oxidation in the blood-plasma.

Classification of Leucocytes.—We have proceeded as far as we could with our analysis of the leucocytes as a unit, and it now becomes necessary to ascertain, if possible, the functions of the various types which histologists, headed by Ehrlich, have established with the aid of staining methods.

Kanthack and Hardy[16] not only give a clear, though succinct, outline of the various varieties of cells, but they emphasize features of the problem which are of special interest to us. After briefly reviewing the more prominent contributions to our knowledge of the subject since Wharton Jones's memoirs, published in 1846, including the investigations of Rindfleisch (1863) and Max Schultze (1865), appeared, they write as follows:—

"After Max Schultze, no further advance was made or, indeed, was possible in the histological analysis of the sporadic mesoblast, until Ehrlich, in 1878, furnished a rational basis for the use of staining reagents by his far-reaching discovery that the elective affinity of certain constituents of tissues for particular stains could be referred to two factors: the *chemical nature* of the staining substance employed and—a point too often neglected by workers who have followed his methods—the nature of the medium in which the stain is dissolved.[17] Ehrlich drew particular attention to the granules, the possession of which characterizes various forms of wandering cells. These, he divided into five classes, differing either in their special affinity for bases, acid, or neutral dyes, or in size. The α or eosinophile granulation colors *only* with acid dyes; the β granulation colors with both acid and basic dyes (amphophile); the γ granulation colors *only* with basic dyes, and the individual granules are large; the δ granulation colors *only* with basic

[16] Kanthack and Hardy: *Loc. cit.*, p. 82.

[17] All the italics are our own.

dyes, but the individual granules are small; and the ε granulation colors *only* in neutral dyes.

"The nomenclature of the granules was extended to the cells bearing them. Thus, the various forms of white cells found by Ehrlich in blood were: I. A small cell free from granules, to which the name lymphocyte was given, from the fact that it appears to be developed in lymphoid tissue. This is the small, non-amœboid form of Max Schultze. II. A cell characterized by possessing fine granules and one or several nuclei. This is by far the most numerous form of white blood-corpuscles in mammalia, and was found by Ehrlich to be neutrophile in man, and amphophile in rabbits and guinea-pigs. III. The eosinophile cell, or coarsely-granular cell of Wharton Jones and Max Schultze. It occurs only in small numbers in the blood of mammalia, but is abundant in the blood of lower vertebrates. IV. A basophile cell with fine basophile granules (δ granulation).

"The mononuclear amœboid cells of Max Schultze are apparently grouped with the neutrophile cells by Ehrlich. In addition to these forms Ehrlich describes a basophile cell with coarse granules (γ granulation), occurring mainly in connective tissues and also in the blood of frogs, but not in the blood of mammals. These he calls 'Mastzellen. . . .'

"From what we have said so far it will be seen that the group of finely-granular blood-corpuscles described by Max Schultze includes the amphophile and neutrophile and the finely-granular basophile cells of Ehrlich. Since Ehrlich's work no contribution to our knowledge of the morphology of the wandering cells has been made except on points of detail. Mention must, however, be made of the group of cells recognized by Metchnikoff[18] in his treatise on inflammation. The term 'leucocyte,' originally applied by the French school of physiologists, is used to designate wandering cells, and the following varieties are recognized: (I) lymphocytes; (II) mononuclear leucocytes with abundant protoplasm and a round nucleus; (III) polynuclear leucocytes, or 'leucocytes neutrophiles'; (IV) eosinophile leucocytes."

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[18] Metchnikoff: *Loc. cit.*

Our purpose being to ascertain the physiological functions of the various types, Ehrlich's four classes, by affording definite microchemical limits, will probably prove more useful than the simplified groupings that other histologists have introduced, and which, by reducing the number of divisions, have tended to efface landmarks that can serve as clues for research. We will preserve, therefore, Ehrlich's classification, and try to ascertain whether the various types of cell do not differ physiologically from one another as they do histologically.

Lymphocytes and Hyaline Cells. — The first cell of the Ehrlich series, the lymphocyte, seems fully entitled to the position accorded it by histologists in general: that of a leucocyte in process of development. The cellular substance is devoid of canaliculi (or net-work of mitoma) and of granules, although the nucleus itself is supplied with both, and is evidently functionally active. Lymphocytes are considerably smaller (6 to 6.5 μ) than leucocytes, and represent less than one-fourth of the total number of these cells. They are devoid of amœboid motion. Hyaline cells have been classed in the same category, the cell-body being likewise free from granules, as shown in Gulland's plate, Fig. 1. Both may become active, however, before complete maturity is reached.

Neutrophile Leucocytes.—These are extremely important members of the leucocyte family, for they represent fully three-fourths of the white cells of the blood, and constitute Metchnikoff's main group of phagocytes. They are termed "neutrophile" by Ehrlich because their granulations stain with both acid and basic dyes. Their reaction to acid dyes is very much less intense, however, than is the case with purely acidophile cells, according to Kanthack and Hardy. Their granules are small as compared to those of other acidophile cells. Though termed "polynuclear" leucocytes by Metchnikoff, the masses thought to represent as many nuclei, are united by thin bridges, thus constituting a single nucleus. Especially is this likely since the only other type of cell deemed phagocytic by Metchnikoff is a mononuclear cell. Gulland contends that no shape of nucleus is invariably associated with granules of a special kind. It seems evident, therefore, that the phagocytic cells are only distinguishable by their affinity for alkaline

dyes and a slight affinity for acid dyes, and by the concurrence of these histological properties with small granules.

Kanthack and Hardy, who refer to this leucocyte as a "finely-granular oxyphile cell," speak of it as follows: "It has a very limited and precise distribution, for, under normal conditions, it is entirely absent from extravascular spaces, and occurs *only in the blood*,[19] where it is by far the most numerous corpuscle, forming 20 to 70 per cent. of the total number of white corpuscles. The fluctuation in this percentage is probably due, in the main, to the great periodic variations in the number of lymphocytes present in the blood. Thus, the effect of a meal is to cause a considerable increase in the number of lymphocytes in the blood, and, therefore, a fall in the share of the total white corpuscles due to finely-granular cells. If this disturbing factor be eliminated," continue these investigators, "and the percentage of the finely-granular oxyphile cells be taken of the adult white corpuscle only, then this is found to be always very high: in man, 75 to 90 per cent."

Metchnikoff, referring to the phagocytic properties of these cells, writes as follows[20]: "Even outside the organism these amœboid cells readily inglobe a large number of foreign particles with which they may come in contact, and they may often be seen literally crammed with all sorts of granules. Like the amœbæ, they swallow not only inert bodies, such as granules of carmine or other substances that are insoluble in the fluid surrounding the leucocytes, but also a large number of living organisms." This is merely quoted to emphasize the fact that the leucocytes differentiated by Ehrlich from all others by the term "neutrophile" are, irrespective of the form of their nucleus, the wandering cells which Metchnikoff has shown to fulfill the physiological function he has termed "phagocytosis."

But the property which these cells so strikingly show, *i.e.*; their ability to ingulf or rather ingest substances of all kinds, seems to us to suggest that they are intrusted with another rôle in the body: *i.e., its nutrition.* In the second chapter we referred to the fact that Macallum had observed, in sections of intestines taken from animals first starved, then fed upon

[19] All italics are our own.

[20] Metchnikoff: *Loc. cit.*, p. 115.

a substance containing albuminate of iron, free leucocytes crowded with granules of iron-pigments, in the intestine. Some of these cells appeared to pass out through the epithelial cells, while others advanced into the subepithelial elements. Macallum had also found them in the venules of the villi, the spleen, etc.

We have just seen the reference of Kanthack and Hardy to the "considerable increase in the number of lymphocytes in the blood, and, therefore, a fall in the share of the total white corpuscles" caused by a meal. Both these two phenomena become normal events instead of a "disturbing factor" if the process of digestion includes the use of a large proportion of adult or fully-developed leucocytes to transport various materials from the intestinal canal to various parts of the organism. It is evident that under these circumstances the immediate neoformation of lymphocytes, and their rapid growth, as is probably their wont, to the state of mature cells, becomes a *sine qua non* of continued existence.

Overlooking the possibility of such a function, and led by his own hypothesis to ascribe to intracellular processes the presence of food-products in the leucocyte, Metchnikoff writes[21]: "The digestion of proteid substances by the leucocytes is well shown by the gradual changes that take place in the muscular fibers which have been inglobed by leucocytes in cases of acute muscular atrophy. The presence of *peptone* in leucocytes, which has been so often proved by Hofmeister, is sufficiently accounted for by this fact of intracellular digestion, and need not, therefore, be referred, as done by this author, to an *absorption* by these cells of the *peptone formed in the alimentary canal.*" We need hardly observe, however, that, added to the foregoing testimony, Hofmeister's view seems sustained.

Indeed, the process to which the peptones owe their presence within the cell is not difficult to trace, if the latter's mechanical functions, as we have construed them, are taken into account. The presence of peptones within the perinuclear vacuole being an accepted fact (since it is recognized by both investigators), the presence therein of substances from which

[21] Metchnikoff: *Loc. cit.*, p. 124.

the peptones are elaborated must be accounted for. Metchnikoff traces these to products of degeneration, as suggested by his comparison, and perhaps to waste-products of digestion. Hofmeister's conception differs only from this in implying a closer or more direct relationship between the leucocytes and the intestinal contents of their host. In other words, while Hofmeister associates leucocytes with the process of digestion, Metchnikoff looks upon them only in the light of scavengers. That phagocytes may fulfill both rôles is obviously suggested, not only by their own chemico-physiological characteristics, but also by their itinerary in the system. Both Hofmeister and Metchnikoff are right, therefore, each in his own way.

In his review of the absorption of proteids Stewart[22] writes: "Although a certain amount of egg-albumin and other native or slightly altered proteid substances can be absorbed as such by the small and even by the large, intestine, there can be no doubt that the greater part of the proteids of the food is first changed into proteoses and peptones. But proteose and peptones are absent from the blood, and, indeed, when injected into the blood they are excreted in the urine. When injected in larger amount they pass also into the lymph, from which they gradually reach the blood again, and are eventually, as before, eliminated by the kidneys. The clear inference is that when absorbed from the alimentary canal they must be changed into one or both of the chief proteids of blood and lymph (serum-albumin and serum-globulin) in their passage through its walls. And it has actually been shown that during digestion of a proteid meal the mucosa of the stomach and intestine contains proteose and peptone, while none is present in the muscular coat or in any other organ. They rapidly disappear from a portion of the mucous membrane kept at a temperature of about 40° C. outside the body; but not if it has been thrown into boiling water immediately after excision, nor even if it has been heated at 60° C. for a few minutes and then kept at 40° C. Now, a temperature of 60° C. does not destroy an unorganized ferment, but kills a *living cell.* The regeneration of the proteose and peptone must, therefore, presumably

[22] Stewart: "Manual of Physiology," fourth edition, 1900.

take place in *cells*, and the only available cells in this locality are those which line the intestine, or the *leucocytes* which wander between them. Accordingly, both have been credited with the power of absorbing and transforming these substances."[23]

If our views concerning the functions of the epithelial cells of the intestines, as submitted in the seventh chapter, are sound, they subserve an entirely different function from that now generally ascribed to them: *i.e.*, that of supplying the intestinal tract with a secretion calculated mainly to asepticize the intestinal contents. On the other hand, we showed that the lymph-follicles, including Peyer's patches, supply leucocytes, formed in the cytogenic area of the follicles (Flemming's central nodule) to the intestinal cavity through the fenestrated membrane overlying each follicle. As our inquiry did not afford evidence to the effect that all these leucocytes served to insure destruction of pathogenic bacteria, we stated that *some* of them carried out this function. Indeed, we had good ground for this limitation, for we had already referred to the iron-laden leucocytes observed by Macallum and we were led later on to allude to those charged with the return of bilirubin to the circulation. That the leucocytes supplied to the intestinal canal by the cytogenic follicular areas, include some—and probably a large proportion—whose functions it is to ingest proteids *with* the iron and bilirubin, then re-enter the intestinal wall by way of the villi, is very likely. To the various agencies thus incorporated in the organism can now be added that referred to by Metchnikoff in the sentence: "The presence of peptones in leucocytes which has been so often proved by Hofmeister." While this contributes further evidence to show that our conception of the whole process must be poised upon solid premises, it also suggests that leucocytes ingest *proteids*, and not peptones, from the intestinal canal, because peptones are the terminal products of the digestion of proteids.

If leucocytes ingest proteids, these must accumulate in their perinuclear vacuole and find their way into the nuclear canaliculi. These cells being freshly supplied to the intestinal

[23] All italics are our own.

canal from the follicles, the proportion of blood-plasma in them must be limited when, laden with proteids, they enter the venules of the villi to find their way to the portal vein. Even in this vessel they must again find a dearth of oxidizing substance, for we have seen that this channel is essentially venous. We must not lose sight of the fact, however, that potent additions to its contents are obtainable here: the spleno-pancreatic internal secretion, *i.e.*, trypsin, to which the plasma of arterial blood and dextrose may be superadded when the precincts of the hepatic artery, *i.e.*, the hepatic lobules, are reached.

If these cells do take up proteids and other bodies utilized in nutrition or in the building up of various organic structures, their own canaliculi, *i.e.*, those of the cell-substance, must serve as the eliminatory channels. In other words, proteids ingulfed by the leucocyte must be submitted to a process of digestion in the nucleus and its vacuole, and the products be passed out as granules. This elevates leucocytes to the rank of glandular organs, but we must not overlook the fact that glands in general supply their secretion in the form of granules. Referring to the parotid, for instance, Professor Foster speaks of the secretion as "generally in the form of granules" and of the "granules" which in the submaxillary gland "may obscure the nuclei." The granules of the pancreas, of the intestinal epithelial cells, etc., are also familiar examples. Indeed, all these granules only differ from those of leucocytes in being less complicated molecularly and smaller. They seem to us fully to represent a true, cellular secretion.

What is the nature of the neutrophile's secretion, *i.e.*, the composition of its granules? Milroy and Malcolm[24] state that the finely-granular amphophile (or neutrophiles) granules "are usually taken to be proteid in nature," and refer to the fact that Sherrington had suggested that they might be "of nucleoproteid nature": a view which their own researches confirm. Under the action of alcohol kept at boiling-point, neither fine nor coarse oxyphile granules were dissolved; ether also at boiling-point gave similar results. These agents being then used successively, the granules remained practically unaltered: a

[24] Milroy and Malcolm: Journal of Physiology, vol. xxv, 1899.

fact which leads the authors to conclude that the granules *cannot consist* of *fat* or *lecithin*. Weak alkaline solution at 115° to 120° C. almost entirely removed the granules from the finely-granular cells, "but the most striking feature was the persistence of two structures, the nuclei and the coarse oxyphile granules." Solutions of sodium carbonate ($^1/_2$ to 1 per cent.), followed by careful washing, almost entirely removed the fine oxyphile granules in from one to sixteen hours, while the coarse ones were left. Oxalic acid (0.4 per cent. in alcohol, then 1 $^1/_4$-per-cent. watery solution) entirely removed the small granules, a few of the coarsely-granular oxyphile cells containing pink-stained granules, while others were vacuolated. As a result of these tests (which should be read *in extenso* in the original paper) Milroy and Malcolm write as follows: "The possibility of both types of granules consisting of the same kind of organic matter either *differently bound* or with organic salts attached in such a way as to alter the solubilities is certainly a strong one. That it is not *simply* albumin or globulin appears evident from the comparatively insoluble character of both types of granules, but especially the coarse oxyphile ones. Again, the fact that the fine granules are not only oxyphile, but also basophile, supports the view that they are composed of a *complex proteid substance*.[25] . . ." The concordance of these facts with those previously recorded appears to us conclusive.

Milroy and Malcolm's researches not only seem to us to give neutrophile granules their own identity (though showing a distinct kinship to the larger acidophile granules), but also to emphasize the fact that these minute masses of proteid substance represent the end-result of the intracellular process that occurs during the journey of the leucocytes from the intestinal villus to the general circulation *via* the portal and hepatic vessels.

Is it only in the cells that the reactions which serve to convert proteids into assimilable products occur? The investigations of Milroy and Malcolm will greatly assist us in elucidating this question.

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[25] The italics are our own.

In their first article on the "Metabolism of Nucleins"[26] these investigators say, in the course of a review of the metabolism of the nucleins under physiological conditions: "When nucleins are taken by the mouth, the first change that they undergo in the alimentary tract is a simple solvent one in the stomach, and that only to a very slight degree. They are never split up into their constituents. They are easily broken up, however, by the *pancreatic secretion*[27] into an organic phosphorus-holding acid (not nucleic acid) and albumose or peptone. The important points to notice are that the phosphorus is still in organic combination, and that neither ortho- nor meta- phosphoric acid is so formed. It is probable that the organic phosphorus-holding acid so formed is similar to thymic acid. It forms soluble compounds with albumose and peptone, and is, in all probability, so absorbed. After absorption the bodies derived from the nucleins cause a well-marked *leucocytosis*, and the excretion of phosphoric acid in the urine is increased. Whether a hypoleucocytosis *always* precedes the hyperleucocytosis is difficult to say. Almost all the writers on this subject have emphasized the fact that, on giving nucleins by the mouth, the phosphoric-acid excretion in the urine is increased; but they have omitted to show that this excretion *cannot be accounted for* by the phosphorus taken in the form of nucleins, there being really more phosphorus excreted by the kidneys than was present in the original nucleins."

Again, as a result of a series of experiments, Milroy and Malcolm are led to the following conclusions among others: "1. The digestion products of nuclein-holding tissues, nuclein and nucleic acid, cause, on being absorbed, a temporary leucocytosis, which is accompanied by a rise in the P_2O_5 excretion above that derivable from the absorbed phosphorus. These alterations are especially well marked after giving nucleic acid. 2. The alloxuric bodies are excreted in excess, after nucleic acid has been given, and in all probability also after large doses of nuclear-holding tissues or nucleins, although in our experiments, owing to the small amount of thymus taken, there was no distinct increase. 3. The uric-acid excretion after nucleic

[26] Milroy and Malcolm: Journal of Physiology, vol. xxiii, No. 3, July 26, 1898.
[27] All italics are our own.

acid was only slightly, if at all, increased. We were exceedingly anxious to give larger doses of nucleic acid, but were unable to do so because of certain rather disagreeable symptoms *(severe muscular tremors)* which arose after the *larger* quantity had been given."

The augmented phosphoric-acid excretion to which the authors refer, and which they state cannot be accounted for by the phosphorus taken in the form of nucleins, has doubtless suggested to the reader as primary cause the increased functional activity of the adrenal system induced by the phosphorus ingested: an interpretation sustained by the presence of severe muscular tremors, "which arose after the larger quantity had been given." Of course, phosphorus here acts like any other toxic as a stimulant, the anterior pituitary body responding to the effects of organic poisons as well as those foreign to the system as a chemical entity.

Still, this involves the necessity of showing that leucocytes are themselves the seat of the enhanced metabolism and the source of the excess of phosphoric acid to which the muscular tremors are due, in accord with our previous statements, to that effect. Again, if, as we have suggested, the granules represent the leucocytic secretion, an excess of granules must occur under the influence of the stimulation of the adrenal system induced. That such is the case is shown by the following casual remark of Stokes and Wegefarth,[28] who, as stated, based their studies of the free granules derived from leucocytes upon examinations of blood taken from about five hundred persons: "In perfectly fresh specimens the granules were not numerous, but they seemed somewhat increased in patients who had been taking *tonics* or various alcoholic drinks."

This, in turn, involves a query as to the manner in which the anterior pituitary body becomes primarily stimulated when nucleins are taken in excess, for it would seem that, locked up in the perinuclear vacuole of the leucocytes, their phosphorus could not influence the adrenal system through the blood-stream. This would doubtless hold were the intracellular process to cease at any time, but, as this must begin as soon

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[28] Stokes and Wegefarth: *Loc. cit.*

as the cells enter the hepatic capillaries, after acquiring therein their adequate supply of oxidizing substance, their normal production of granules must start at once. An inordinate proportion of nucleins in the food soon supplies the blood-stream, through the agency of the cells, with an abnormal quantity of these minute phosphorus-laden bodies. These at first give rise to excessive functional activity, including among other signs the "severe muscular tremors" to which Milroy and Malcolm refer, coupled with an excess of P_2O_5 production. Persisted in, however, the excessive (relative) ingestion of nucleins brings on, as do other toxics, adrenal insufficiency, which, by entailing a reduced production of oxidizing substance and trypsin upon which the physiologically perfect intracellular reactions mainly depend, correspondingly lowers the efficiency of the cleavage-processes. This means, instead of the physiologically perfect granules which, we have seen, Milroy and Malcolm found to be proteid in nature, an accumulation in the blood of proteid toxalbumins.

In their first paper, the above-mentioned investigators draw attention to the two decomposition products considered "as more or less characteristic signs of the decomposition of the nucleins, viz.: the alloxur bases and phosphoric acid." If our conception as outlined in the preceding paragraph is justified, these alloxuric bases are products of *inadequate* metabolism, while phosphoric acid is the product of perfect metabolism. Uric acid having likewise been considered by us as a product of the complete process, a rise of alloxuric excretion cannot occur along with excessive phosphoric-acid production. That our conclusion, based mainly on Horbaczewski's work, was warranted, is shown by what Milroy and Malcolm term "points of special importance" as results of a series of experiments, namely: "1. There is no doubt that the P_2O_5 excretion is increased even when very small doses of thymus are given. 2. Relatively, also, the P_2O_5 is increased in proportion to the nitrogen. 3. With the small amount of thymus taken there was practically no appreciable alteration in the excretion of the alloxuric bodies, either absolutely or relatively to the total nitrogen or total P_2O_5." All this serves to emphasize another feature of the problem: *i.e.*, that *phosphoric acid is the proto-*

type of uric acid as a product of perfect or physiological intracellular metabolism, and that the phagocytic leucocytes which take up nucleo-proteids from the intestinal food-products are the seat of the reactions through which these bodies are converted into assimilable products, i.e., peptones.

Although we have only dealt so far, as regards the intracellular processes with which nucleo-proteids are concerned, with neutrophile leucocytes, these are not alone the seat of reactions which, normally performed, end in the production of uric and phosphoric acids. Indeed, we have seen that all leucocytes contain nuclein in their "nucleus" — a fitting name under the circumstances, and the physio-chemical process reviewed only typifies that which occurs in all varieties of leucocytes. Wherein the neutrophile cells are distinguishable, however, is in their ability as phagocytes to take up nucleo-proteids from the intestine, and to break them up, by means of the trypsin and oxidizing substance subsequently absorbed by them, into peptone and an organic compound containing phosphorus.

How are the various bodies, the presence of which this suggests, utilized? The presence of pancreatic secretion in the intestine, and of the spleno-pancreatic secretion in the portal vein, would suggest that the leucocytes must be carriers of carbohydrates: an important question when we consider the leading functional rôle which myosinogen plays in muscular contraction. Dextrose, formed from glycogen, itself in turn a product derived from starches, forms part of a chain of events which would, in a measure, have to occur within the cell itself. That such is the case is suggested by the investigations of Zabolotny,[29] who found that phagocytes devoured particles of starch-paste and digested them: features which led this investigator to conclude that "the presence of an amylolytic ferment in the phagocytes cannot be doubted." But Zabolotny likewise states that when leucocytes ingest starch they become iodophile. This, as is well known, has been termed by Ranvier and other physiologists the "*glycogen* reaction."

Foster, referring to this question, says: "In the case of many corpuscles at all events, we have evidence of the presence

[29] Zabolotny: Russian Archives of Pathology, April, 1900.

of a member of the large group of *carbohydrates*, comprising starches and sugars, viz.: the starch-like body *glycogen*. . . . This glycogen may exist in the living corpuscle as glycogen, but it is very apt, after the death of the corpuscles, to become changed by hydration into some form of sugar, such as maltose or dextrose." Indeed, he furnishes us complementary evidence, alluding to the cellular proteids in the following sentence: "One of these proteids is a body either identical with or closely allied to the proteid called *myosin*, which we shall have to study more fully in connection with muscular tissue." We have shown that myosin is the *post-mortem* product of the action of what remains of oxygen in the plasma upon myosinogen, and that this is the cause of *rigor mortis*. Professor Foster says, in this connection: "And we have reasons for thinking that in the living white corpuscle there does exist a body identical with or allied to *myosinogen*, which we may speak of as being in a fluid condition, and which, on the death of the corpuscle, is converted, by a kind of clotting, into myosin, or into an allied body which, being solid, gives the body of the corpuscle a stiffness and rigidity which it did not possess during life." All this seems to us to clearly suggest that these leucocytes, in the light of our views, supply the muscle-cells of the entire organism with myosinogen.

Still, our analysis alone so far points to the neutrophiles —by far the most numerous leucocytes in the blood-stream— as the ones upon which this great function would devolve. We deemed it necessary, therefore, to control this conclusion by showing that excessive muscular exercise, by creating a demand for myosinogen in the cells of all muscles,—skeletal, cardiac, vascular, etc.,—engenders a leucocytosis in which the neutrophiles prevail. We were fortunate enough to find a study of this subject by R. C. Larrabee,[30] who writes as follows: "The paper is based on a study of the blood of four of the contestants in the Boston Athletic Association's Marathon race of 1901. This is a road-race of about twenty-five miles (40 kilometers), held each spring. The severity of the contest will be apparent when it is said that the winner—not included in my four—

[30] R. C. Larrabee: Journal of Medical Research, Jan., 1902.

covered the distance in less than two and one-half hours. This is about ten miles an hour, about as fast as an ordinary man rides his bicycle for pleasure. . . . The blood of these four cases [counted by the author, assisted by Dr. W. H. McBain] before the race showed no abnormalities. The percentage of polymorphonuclear neutrophiles may perhaps run a little high, but this is to be expected in active young men in the best possible physical condition. After the race the blood was taken immediately, within five minutes from the actual finish. In every case a leucocytosis was found, varying from 14,400 to 22,200. The differential count showed that the increase was *mainly* in the polymorphonuclear *neutrophiles*."

That the exciting cause of the leucocytosis was the increase of waste-products, which in turn stimulated the adrenal system, hardly needs to be dwelt upon. Vagal influence incited to inordinate activity and controlled the organs charged with the genesis of these particular cells, while the inordinate oxidation processes started by the overactive adrenals in all tissues accounts for the general leucocytosis which the word "mainly" implies.

Myosinogen being a member of the globulin group of proteids, the other members of this group should be represented among the cell's products, particularly fibrinogen found in the blood-plasma in association with serum-globulin and serum-albumin. That such is the case seems evident. Stewart[31] alludes to the sources of nucleo-proteid in the following words: "In shed and clotting blood, the only possible sources of nucleo-proteid, so far as we know, are the corpuscles and the blood-plates. The red corpuscles we may at once dismiss, for, although they contain a small amount of nucleo-proteid, not only do they remain intact under ordinary circumstances during coagulation, but there is the strongest evidence, as has already been pointed out, that they do not make any essential contribution to the process. We have left over the leucocytes and the platelets. The latter are said and the former are known to yield *nucleo-proteids* when they are broken up in the laboratory; and it is highly probable that from both, but especially

[31] Stewart: *Loc. cit.*

from the white corpuscles, nucleo-proteid is liberated in the first moments after blood is shed, and that this nucleo-proteid *is then changed into fibrin-ferment.*"

The relationship between the cellular nucleo-proteids and fibrin which this quotation suggests finds itself sustained by Ranvier,[32] who, alluding to the rôle of granules in the formation of fibrin, says: "Free granulations, which we found in the blood besides the red and white corpuscles, are very numerous; they were termed 'elementary vesicles' by Zimmermann. In a preparation of human blood examined after rouleaux of red corpuscles have formed these granulations may easily be observed, two varieties being distinguishable. The first are spherical, small droplets of fat; the others are angular or variable in shape, and appear at first as if they were fragments of white corpuscles, but differ from the latter in not being altered by water. They are *stained by iodine*, but remain colorless in carmine solutions. We will see that these are also the characteristics of fibrin." After reviewing the phenomena that attend coagulation, and exposure by washing of the fibrinous net-work, he says: "When this preparation is examined and magnified four hundred to five hundred diameters, the fibrinous reticulum can be seen distinctly, and is disposed in a very interesting manner: From an angular granulation, from 1 to 10 μ in diameter, very tenuous fibrils start divergingly, then subdivide, to unite with other fibrils, in order to form a delicate net-work. The preparation is covered with these small net-works, each of which has its central granulation. . . . The granulations which serve as centers for each diminutive fibrinous reticulum have the same microchemical properties as the fibrils."

A normal deduction which seems to us to impose itself in this connection is that fibrin is to the blood what myosin is to the muscle-cells, *i.e.*, a post-mortem product due to arrest of the oxidation process which during life is insured by the oxidizing substance—the supposed "fibrin-ferment." In other words, it not only becomes evident that *peptones, myosinogen, and fibrinogen are products of the same variety of leucocyte, the neutrophile, and therefore chemically similar when liberated from*

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[32] Ranvier: *Loc. cit.*, 213.

the latter, but also that *fibrinogen subserves the same purpose in the blood that myosinogen does in muscle: i.e., it supplies it with its primary source of functional energy.*

True, the solubility of fibrin differs somewhat from that of myosin, but this is probably due not to a difference in the molecular structure of fibrinogen as against that of myosinogen, but to the influence of the medium in which the granules are dropped by the leucocyte. Indeed, the ashes of fibrin contain a larger proportion of calcium and magnesium phosphate than does myosinogen.

Another conclusion which now seems to us warranted is that *the neutrophile leucocytes are the agencies which take up proteids in the intestinal canal, and, after submitting them to a process in which various physio-chemical bodies taken up by them in the portal and hepatic systems take part, distribute the products to every part of the organism, including the blood itself.*

Such being the case, the proteids, inclosed in their diminutive carriers, should not be found in the blood of the portal system. Professor Foster writes, in this connection, after referring to the difficulties attending the experimental determination of the path taken by proteids: "Bearing this in mind, we may state that all observers are agreed that peptone is absent from chyle, or at least that its presence cannot be satisfactorily proved. On the other hand, while some observers have succeeded in finding peptone in the portal blood after food, but not during fasting, many have failed to demonstrate the presence of peptone in the blood either of the portal vein or of the vessels at large, *even after a meal containing large quantities of proteids.*" Again: "If an artificial circulation of blood be kept up in the mesenteric arteries supplying a loop of intestine removed from the body, the loop may be kept alive for some considerable time. During this survival a considerable quantity of peptone placed in the cavity of the loop will disappear: *i.e.,* will be absorbed, but *cannot be recovered from the blood* which is being used for the artificial circulation, and which escapes from the veins after traversing the intestinal capillaries. The disappearance is *not due to any action of the blood itself,* for peptone introduced into the blood before it is driven through the mesenteric arteries in the experiment may be re-

covered from the blood as it escapes from the mesenteric veins. It would seem as if the peptone were changed before it actually gets from the interior of the intestine into the interior of the capillaries."[33] If our views are sound, *the peptones are hidden in the neutrophile leucocytes which the follicles of the segment continue to produce. These cells, after migrating over the serum-bathed (and thus constantly asepticized) epithelial surface, and ingesting their burden, find their way into the villi's venules and thence into the mesenteric channels.*

If the foregoing analysis and the various deductions submitted are sound, the neutrophile leucocytes must fulfill a rôle in the organism commensurate with their relative proportion in the blood-stream. Indeed, the following conclusion seems to us to have been sustained:—

The neutrophile leucocytes, through the intermediary of their granules, the β granulations of Ehrlich, supply (1) the blood and all tissues (excepting the nervous system) their nutritive elements: i.e., peptones; and (2) the muscles and the blood, the compounds from which they obtain their mechanical energy when exposed to the action of the oxidizing substance: i.e., myosinogen and fibrinogen.

Ehrlich's Eosinophile Leucocytes.—Metchnikoff does not grant Ehrlich's eosinophiles phagocytic properties, these cells being unable to inglobe foreign bodies. Again, as emphasized by Ehrlich, the granules of these cells are only stainable with acid dyes, the other varieties either taking only alkaline dyes or simultaneously, as does the neutrophile just reviewed, both acid and alkaline dyes, etc. This marked affinity for acids obviously gives the eosinophile an identity of its own, while its non-phagocytic functions as clearly separate it from the finely granular cell just reviewed, which is essentially phagocytic. Ehrlich's eosinophile is usually considered under the heading of "coarsely-granular oxyphile cell."

These cells only represent from 2 to 4 per cent. of all the leucocytes in the blood-stream, but this proportion is rapidly increased during disease. Kanthack and Hardy, in the article previously quoted, describe them as follows: "The coarsely-

[33] All italics are our own.

granular oxyphile cell, or eosinophile cell, varies in size in different animals, not only absolutely, but relatively to the dimensions of the other classes of cells. In man it is larger than either the hyaline cell, the finely-granular oxyphile cell, or the finely-granular basophile cell. In the rat, rabbit, and guinea-pig, on the other hand, it is smaller than the largest hyaline cells, but larger than the finely-granular oxyphile and basophile cells.

"The *nucleus* is typically an elongated body bent to form a horseshoe. In the rat the arms of the horseshoe are carried so far round that in film preparations the ends often overlap, giving to the nucleus the appearance of a circle with a large hole in the center. Sometimes the nucleus is lobed; but we are inclined to regard this appearance as being largely due to the stresses to which the nucleus is subjected when the cell is dying. In the living cell at rest, when it is spherical, the shape of the nucleus, so far as it can be determined by the disposition of the cell-granules, is a simple horseshoe or crescent. A distinct nuclear net-work is present.

"*Cell-granules.* — The cell-granules are relatively large, spherical, or slightly ovoid bodies, and are sharply marked off from the cell-substance by their *very high refractive index*, which is so great that in fluid preparations the granules have a *brilliant, greenish luster.*[34] The cell-substance in which they are imbedded has the appearance of a clear, transparent, structureless jelly. The intensity of the oxyphile reaction of these granules differs in different animals, but is always high. Thus, it is very high in the case of the granules of man, these staining with eosin dissolved in 95-per-cent. alcohol. . . . The granules also stain with weak acid dyes, such as Orange *G*, hæmatoxylin, and sodium sulphindigotate. Ehrlich-Biondi's mixture (washed out with 95-per-cent. spirit) colors these bodies brown-purple, and the 'neutral' mixture (washed out with water) stains them a very intense purple. Corrosive sublimate increases the oxyphile reaction, as does also heat when applied to the dried film."

Gulland found Heidenhain's iron-hæmatoxylin extremely

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[34] All italics other than those of the side headings are our own.

valuable to counteract "the bright refraction of the granules" which "blinds the eye to the presence of the threads" (our canaliculi). The granules are stained opaquely in shades of black and gray. He was thus able to ascertain that the granules varied greatly as to size, the smallest granules lying close to the astrophere and the larger at the periphery, the arrangement pointed out by Heidenhain and shown in Figs. 10, 12, and 16 of Gulland's plate. In the newt's blood, as already stated, "these cells are markedly amœboid, and have the habit of throwing out circular pseudopodia, which are often connected to the main part of the cell only by a very delicate thread." Gulland illustrates this feature in Figs. 3 and 6 of his plate, and states that "it is evident that the threads are often broken through and the spherical portion of the cell-body set free, as the blood contains a large number of them." He also refers to the fact that, "when the eosinophile cells are found degenerated in blood or pus examined in the fresh state, the granules are always in the Brownian movement."

In our study of the granules of neutrophile cells we referred to the chemical analysis of Milroy and Malcolm and to various points of dissimilarity between these cells and the coarse oxyphiles now in question. Considered from the standpoint of the latter, these investigations showed that, while neither alcohol nor ether, nor both of these agents used successively, produced alterations in either variety, the failure of the latter process *excluded* the possibility of their consisting of *fat* or *lecithin*. Weak alkaline solutions at about 120° C. caused (a feature referred to by the authors as striking) the removal of practically all the granules of the finely-granular cells (the neutrophiles), and "persistence of two structures, the nuclei and the coarse oxyphile granules." Acetic acid in alcoholic solution and oxalic acid caused partial removal of both granules, but "sodium ethylate in alcoholic solution removed the fine oxyphile granules almost completely and only affected the coarse ones to a slight extent."

The authors, while concluding that the granules might also be nucleo-proteid in nature, *i.e.*, similar to those of the neutrophile cells, account for the discrepancies in the results of their analyses by the following argument: "The fact that weak acid

solutions dissolve both types of granules at least partially is not against the view that they are nucleo-proteid in nature, because these bodies are more easily soluble in weak acid solutions than almost any other complex proteid. The fact that some granules are undissolved, while others are removed, is probably due to the fact that the former have undergone coagulation, while the latter have been rapidly fixed, although it may be also due to the nature of the salts which are combined with the proteid."

Still, the very high refractive index to which Kanthack and Hardy and Gulland refer is not characteristic of the neutrophile granules, and this seems to us to testify against an absolute functional similarity between them and the granules of the eosinophiles. Indeed, with the plasma as excipient for the oxidizing substance, we can as readily account for the presence of the "brilliant, greenish luster" witnessed by the above authors as we can for the phosphorescence of the photogenic organs of lightning-bugs: *i.e.*, by the simultaneous presence of phosphorus and oxygen. This seems to us to indicate that we are dealing with a nucleo-proteid body, as Milroy and Malcolm contend, but with one richer in phosphorus than that forming the neutrophile granules.

What are the functions of the eosinophile leucocytes in the organism? The high percentage of phosphorus in their granules suggests the possibility of their being lecithin-carriers; but we have seen that the investigations of Milroy and Malcolm clearly show that this organic body is absent. L. F. Barker,[35] of Baltimore, noted the presence of iron in the granules of the eosinophile leucocytes,—a point which he thinks may be of some value in determining the significance of the leucocytic granulations,—but we cannot consider them as the cells intrusted with transportation of iron from the intestine, for they are not phagocytic. Indeed, it has now become evident that the neutrophiles are intrusted with this function, for Macallum used albuminate of iron. The intestinal leucocytes of his previously starved animals evidently took this substance up as they would the proteids of their usual food. Barker's

[35] L. F. Barker: Johns Hopkins Hospital Bulletin, Oct., 1894.

observation, however, adds another link to the chain of evidence which unites the eosinophiles to the neutrophiles, for, in addition to being both nucleo-proteid carriers, they now become also iron-carriers. By tracing the itinerary of this iron we may, therefore, obtain a clue to the true identity of its cellular host.

The phagocytes seen by Macallum to ingest the albuminate of iron, being assimilated to those charged at all times with the duty of selecting proteids from the intestinal foodstuffs, it becomes a question as to where they can part with their iron in order to facilitate its absorption into the hæmoglobin molecule, of which, as is well known, it forms an important constituent. From the intestine the iron is carried to the portal system, thence into the hepatic lobule. It must be here that the phagocytic leucocytes must take part in some process related to the elaboration of hæmoglobin, for we have seen on page 335 that in the spleen the leucocytes are formed *in situ*, pass out into the pulp-channels, take up the iron-pigment (probably that of disorganized red corpuscles), and carry it to the liver. Again, and for reasons which are there given, we were led to conclude (page 339) that bilirubin and iron were used to build up the hæmoglobin in the lobular (hepatic) capillaries. The liver, therefore, seems to receive iron from both directions—intestine and spleen—a normal mechanism when we consider that the liver's blood passes almost directly to the heart, and thence to the lungs.

How do the eosinophile *(non-phagocytic)* leucocytes acquire their iron? We can hardly imagine that when the splenic or intestinal leucocytes reach the hepatic lobule their contents or any part thereof is disgorged to enable another cell to appropriate it. Indeed, there is not the slightest evidence that such a process occurs, although the eosinophile has already been shown to contain not only iron, but also the other main constituents of the neutrophile cell. There exists a physiological process, however, through which the eosinophile can acquire all the attributes of the latter: *i.e.*, by mitosis, a mode of cell-multiplication known to apply to leucocytes and particularly to neutrophiles. Gulland refers to this feature in the following lines: "The cells which one sees dividing or about

to divide have generally the appearance of medium-sized hyaline cells, with a relatively large rounded nucleus and a comparatively small cell-body in which the mitoma is not easily made out. But there is no doubt that cells with horseshoe-shaped nuclei [the eosinophiles] divide, and that the nuclei may even advance as far as the spirem stage without altering their shape. Cells with more markedly polymorphous nuclei, as, for instance, the *ordinary oxyphile cells*, certainly divide also, but they seem generally to go through a preliminary resting stage in which the polymorphous nucleus returns to the rounded form."

In Gulland's plate, Figs. 3 and 6, which refer to eosinophiles from newt's blood, graphically portray a secondary process through which these cells can subdivide, or rather yield a portion of their substance. In 3, a spherical pseudopod is in the act of being formed; in 6, three similar masses appear, the lowest of which is on the point of being separated by the mother-cell. Referring to the bridges that connect net-works of granules with basophile leucocytes, Gulland remarks: "I have little doubt that when that stage is reached [he associates the phenomenon with a supposed process of degeneration] these bridges are torn across and the granules are actually left behind. This forms an exact parallel to what happens in the *eosinophiles* of the newt's blood."

It thus becomes evident that recognized cytological phenomena sustain the conclusion that *neutrophile leucocytes are the parent-cells of eosinophile leucocytes*, and that *eosinophiles can part with segments of their cell-substance.*

But does the process of neutrophilic mitosis actually occur in the liver? M. Duval,[36] in his study of the hæmatopoietic functions of this organ, refers to the proportion of the red to the white corpuscles in the blood of the portal vein as compared to that in the hepatic vein, and writes: "Researches in this connection give as result: 1 white corpuscle to 746 red in the *portal* vein, and 1 white corpuscle to 170 red in the *sub-hepatic* veins. This difference can only be due to a production of white corpuscles in the liver or to a destruction of red cor-

[36] M. Duval: "Cours de Physiologie," p. 200.

puscles." That red-corpuscle destruction is a function of the spleen is sustained by the presence "in the spleen-pulp," using Foster's words, of red corpuscles "in various stages of disorganization, some of them lying within the substance of large colorless corpuscles, and, as it were, being eaten by them." The presence of blood-pigments in the liver has been thought to indicate that red corpuscles were destroyed in this organ; we have seen, on the contrary, that it is the seat of a reconstructive process of which hæmoglobin is the product. Though the liver may be a seat of destruction for red-cell fragments, the likelihood that any entire corpuscle leaves the capillaries of the hepatic lobules to penetrate the cells is so remote that it can be left out of question. On the other hand, we have seen that these capillaries are the seat of the more important processes connected with the blood. It seems evident to us, therefore, that the liver, owing in part to the inordinate temperature of its lobular channels (106° F.; 41.9° C.), is also the seat of the mitotic process.

"At a certain period," write Böhm, Davidoff, and Huber,[37] "the embryonic blood consists principally of nucleated red cells, which proliferate in the circulation by indirect division. The colorless blood-cells, the development of which is not yet fully understood, appear later. It is possible that they also are elements of the blood-islands, which do not contain any hæmoglobin. In a later period of embryonic life the liver becomes a blood-forming organ. Recent investigations have shown, however, that it does not take a direct part in the formation of the blood, but only serves as an area in which the *blood-corpuscles proliferate* during their slow passage through its vessels. The *blind, sac-like endings of the venous capillaries* seem to be particularly adapted for this purpose, as in them the blood-current stagnates, and it is here that the greater number of blood-cells reveal mitotic figures. The newly-formed elements are finally swept away by the blood-stream and enter the general circulation (Van der Stricht, 92; v. Kostanecki, 92, III)."

Gulland likewise states that the eosinophile cell is derived from the "finely-granular acidophile" (the neutrophile), and

[37] Böhm, Davidoff, and Huber: *Loc. cit.*, p. 168.

the latter is itself traced back to the lymphocyte. "The transition-forms between the finely-granular and the coarsely-granular acidophile cells are seen much more frequently in the bone-marrow than in the blood," says this investigator, "and it seems certain that both from this source and from mitotic division the main source of the eosinophile cells is in the bone-marrow." That there is ample margin for our view that mitosis may occur in the liver is also suggested by the following additional lines: "They must arise *elsewhere*, however, *in abundance*,[38] for Schaffer[39] and I[40] have shown that they are present in the thymus and in lymphatic glands before either bone or bone-marrow is properly formed at all, and Engel[41] has seen them in the chick's blood on the fifth day of incubation. In the transition-forms (see Figs. 2, 8, 11) there is little in the general shape of the cell and nucleus to distinguish them from the preceding stage." All the evidence tends to show, therefore, that *the process of mitosis through which eosinophile leucocytes are formed from neutrophile leucocytes, is carried on in the capillaries of the hepatic lobules, though it can also occur elsewhere in the organism.*

We have referred to the direct path which leucocytes can follow from the liver to the heart and thence to the lungs. If eosinophiles are formed in the liver, therefore, the lungs should show indications of the presence of these leucocytes. Proof that such is actually the case is obtainable with the aid of pathology: *i.e.*, the significant fact that in several pulmonary diseases eosinophile cells are to be found in the sputum. Teichmüller,[42] for instance, has not only found this to be the case in pulmonary tuberculosis, but considers an increase of these cells favorable from the standpoint of prognosis. In asthma, though a non-ulcerative process is present, eosinophiles are to be found in abundance in the sputum, and Gollasch[43] states that they are connected with the formation of the Charcot-Leyden crystals.

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[38] The italics are our own.

[39] Schaffer: Centralbl. für die med. Wissen., 1891.

[40] Gulland: Journal of Path. and Bacteriol., 1894.

[41] Engel: Archiv f. mikr. Anat., vol. lxiv, 1894.

[42] H. Lenhartz: "Manual of Clinical Microscopy," advance pages of translation by H. T. Brooks, Post-graduate, July, 1902.

[43] Gollasch: Fortschritte der Med., vol. 1889.

Lenhartz[44] states that "it is not improbable that the majority of cells designated as 'alveolar epithelia' are variously altered forms of leucocytes. The protoplasm very frequently shows fine or *coarsely-granular* fatty metamorphosis, which is characterized by the *strongly refractive index.*"

The irregularity of the granules, and the manner in which they form fibrin, as described by Ranvier, and the peculiar color of the granules is recalled by the following description of the Charcot-Leyden crystals by Lenhartz: "The Charcot-Leyden crystals are delicate, very sharply pointed octahedra which occur in very variable size. They present a sometimes water-clear, transparent, sometimes a slightly yellowish-green, Rhine-wine color; they occur either isolated or in dense collections, which here and there are jumbled together, or in uniform rows, following the mucous shreds." The same author also says: "The crystals were first found in the sputum by Friedreich in croupous bronchitis. On the other hand, Leyden had drawn attention to their frequent occurrence in asthmatic expectoration."

The association with various pulmonary diseases obviously suggests that their presence is pathological, whereas we consider their presence in the lung as normal, and their *elimination* in their recognizable form as an accompaniment of the morbid state. That such is the case is shown by the fact emphasized by Lenhartz that: "The longer the asthmatic subject *is free from* paroxysms,—that is, the more time allowed for the formation of the crystals,—the more densely the spirals are studded with these crystals."

While all these facts sustain our opinion that the lungs show ample evidence of the presence in them of eosinophile cells and of their granules, their identity as offsprings of the neutrophiles should be demonstrable here, as elsewhere, through their chemical properties. Indeed, their identity as daughter-cells of neutrophile leucocytes does not disappear even in the lungs, for both acids and alkalies can dissolve them, while the test common to both neutrophile and eosinophile granules, *i.e.*, insolubility in alcohol, is also applicable here.

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[44] Lenhartz: *Loc. cit.*

Lenhartz not only confirms this assertion by saying, in reference to the crystals: "They are readily dissolved in warm water, acids, and alkalies, but are *insoluble*[45] in alcohol"; but we also, it seems to us, can consider, as confirmation of our interpretation of the identity of the granules from which the crystals were derived, his statement that: "fixation of the air-dried preparation for one hour in absolute alcohol and subsequent staining with Chenzinsky's *eosin*-methylene-blue solution also gives very good results."

All these facts further confirm the origin of the eosinophile leucocytes from the liver, for there is no other path that would have brought them to the lungs. They also seem to us to clearly show that, *after their formation by mitosis in the liver, eosinophile leucocytes are carried to the pulmonary lobules.*

What are the physiological functions of eosinophile leucocytes? In the ninth chapter (page 481) we suggested that the nervo-vascular mechanism of the lungs was composed of two *autonomous*, though correlated, systems: the *respiratory* and bronchial. The respiratory system, according to our conception, is composed of *(a)* the pulmonary *lobules*, in the walls of which the blood is oxygenated; *(b)* the pulmonary artery and its subdivisions, which bring venous blood, adrenal secretion, and hepatic sugar to the capillaries of the *lobules; (c)* the pulmonary venules and veins, which return the arterialized blood to the heart. The bronchial nervo-vascular system, on the other hand, has for its purpose to supply the oxidizing substance, which, by meeting the hepatic sugar contained in the blood of the lobular capillary, liberates the necessary energy upon which the local functions depend. It thus becomes evident that the lobule is the seat of the respiratory process, and that all correlated organs of the respiratory system, from the nasal cavities down to the terminal bronchial ramifications, are but accessory structures.

This question has already engaged the attention of pathologists, including Virchow, Wagner, and Cohnheim. Lenhartz's view is fully sustained by our own investigations, however, when he says: "It is not improbable that the majority of the

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[45] These italics are Dr. Lenhartz's.

cells designated as *'alveolar* epithelia' are variously altered forms of leucocytes. The protoplasm very frequently shows *fine-* or *coarsely-* granular fatty metamorphosis, and is characterized by the strongly *refractive index.*" Again, while Lenhartz expresses his belief that the positive identification of the "alveolar epithelia" is "extremely difficult," he states that he understands thereby "the large oval or round polygonal cells, three to six times as large as a white blood-corpuscle, which are found in almost every sputum. The usually large cell-body is *coarsely granular,* and contains one or several vesicle-like nuclei." The true identity of epithelium of the alveoli and, therefore, of the lobule of which they form part, now seems clear, if interpreted in the light of the data we have submitted: The cells to which Lenhartz refers, *i.e., the lobular epithelial cells, are aggregates of the polynuclear neutrophiles and of the daughter-cells of the latter, the eosinophiles.*

We have seen that the neutrophiles start from the intestinal canal; that Macallum and L. F. Barker found leucocytes gorged with iron in this region; and, finally, that *some* bilirubin at least is recovered from the intestine—obviously, now, by leucocytes. We have traced the latter from the intestinal canal, through the portal system, liver, hepatic veins, heart, thence to the alveoli. After giving the formula of hæmoglobin, Professor Foster writes: "It will thus be seen that hæmoglobin contains, in addition to the other elements usually present in *proteid* substances, a certain amount of *iron;* that is to say, the element iron is a distinct part of the hæmoglobin molecule, a fact which of itself renders hæmoglobin remarkable among the chemical substances present in the animal body." Kanthack and Hardy noted, as previously stated, that "in fluid preparations the granules have a brilliant, greenish luster"—a characteristic of fine hæmoglobin crystals. Hæmoglobin is readily soluble in blood-serum, as are the granules, we have seen. Ether coagulates hæmoglobin; it caused, in Milroy and Malcolm's experiments,[46] the granules to lose a part of their refractive power, even when boiling ether was used. The proteid constituents of the granules of the neutrophiles, myosinogen and fibrinogen, belong to the globulin group.

[46] Milroy and Malcolm: *Loc. cit.,* p. 112.

This recalls our statement (page 440) in respect to the manner in which the heart-muscle is supplied with its myosinogen. We then said, referring to the present analysis: "Paradoxical as the statement may seem, we were led to conclude that the minute granules referred to on page 433"—a general outline of the prevailing views concerning the histology of the myocardium, in which the minute pigment-granules, easily seen therein microscopically, are mentioned—"were actually supplied to the heart through the intermediary of leucocytes. These cells were found to migrate from the liver (also through the hepatic veins) to the inferior vena cava, where they meet the adrenal secretion and proceed with it to the right ventricle."

We can now readily understand how the granules of the neutrophiles are supplied to the muscle-fibers by quoting another of our own statements (page 434) concerning the distribution of fluids in the intimate structure of the heart: "Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. The canals—the lacunæ of Henle—are the intervals *between* the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the *lymphatic vessels;* the lacunæ have been considered as adjuncts, or *extensions,* of the latter." In this sense, therefore, the Thebesian channels are adjuncts of the lymphatic system, for it is through their intermediary that the lacunæ of Henle are supplied with myosinogen granules and —a feature we wish to emphasize—their nutritional peptones and their fibrinogen. All of these jointly supply the heart with its working energy, when acted upon by the oxidizing substance of the blood-stream.

The bulk of the venous blood which enters the heart is sent, we have seen, along with its adrenal secretion and its leucocytes—neutrophile and eosinophile—to the lungs, Virchow, Friedreich, Leyden, Cohnheim, Wagner, Lenhartz, and other investigators having found them in the sputum, and histology

having demonstrated their presence in the alveoli. Again, the path for these leucocytes from the intestine to the true respiratory areas of the lungs is comparatively direct: features which distinctly suggest that the protective functions in the respiratory tract resemble those in the intestinal canal, as regards the eosinophilic granules and the phagocytic functions of the neutrophiles, both kinds of cells being present, as we have seen. Of course, the intestinal lymph-follicles being the source of these cells, another arrangement prevails in the pulmonary lobules: *i.e.*, that to which we referred on page 713, to the effect that the lobular epithelium *per se* is an aggregate of neutrophiles and eosinophiles.

We can readily understand, now, why the eosinophiles deplete themselves of their granules in the alveoli: *i.e.*, to dissolve them in the plasma prior to their absorption by the red corpuscles. Indeed, the reticular structure of red corpuscles, "the same as that of colorless blood-corpuscles,"[47] observed by Louis Elsberg in 1879, seems to us to present all the features that have led us to consider as canaliculi the threads that constitute this reticulum in the latter cells. That the red-corpuscle "granulations," "platelets," or "hæmatoblasts" derived from them are mere droplets of oxidizing substance poured out through these canaliculi is shown by the fact that the characteristic affinity (requiring oxygen and alkaline salts, according to Ehrlich) for methylene-blue again appears: *i.e.*, as manifested by the deep-blue stain which we found in other structures, the axis-cylinder, neuroglia, etc., and in the leucocytes themselves. This fact was also noted by Litten.[48] That the droplets pass out through centrifugal channels in the cell, and that the latter presents the general mechanical characteristics of leucocytes, is also suggested by the researches of Hirschfeld,[49] who observed that the "blood-plates" are first seen as circular disks occupying the center of the cell, then move very slowly toward the periphery, and finally drop out of the cell through a minute aperture, which closes up again.

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[47] M. L. Holbrook: "Proceedings of the American Microscopical Society," vol. 1894.

[48] Litten: Deutsche med. Wochenschrift, Nov. 2, 1899.

[49] Hirschfeld: Virchow's Archiv, vol. clxvi, 1901.

As the "plate" leaves the cell the external portion gradually increases in size and is connected with the rest by a thread. Several of these may leave the cell together from different parts of the periphery. He also found them to stain with methylene-blue and hæmatoxylin. It is evident that we have in the red corpuscle a diminutive nucleated sponge capable of absorbing hæmoglobin from the serum of the pulmonary alveoli and of dealing it out in the blood-stream as needed by the plasma.

This feature and the functions of the leucocytes just described introduce complemental factors in the respiratory process as we interpreted it in the second chapter. It now seems to us that the whole process is summarized in the following conclusions:—

1. The true respiratory areas in the pulmonary lobules are composed of the alveolar endothelial plates (the non-nucleated epithelium) and groups of eosinophile leucocytes (the nucleated epithelium) interposed between the former.

2. The eosinophile cells are the bodies in which hæmoglobin is formed from the proteids, bilirubin, and iron, absorbed by their parent-cells, the neutrophiles, in the intestinal canal.

3. When the eosinophile leucocytes reach the alveoli from the liver via the heart they assume an orderly arrangement and alter their shape, so as to form the alveolar epithelium.

4. The eosinophile leucocytes supply the adjacent plasma with their hæmoglobin, and the latter is absorbed by the underlying red corpuscles along with the oxygenized secretion (oxidizing substance).

5. Leucocytogenesis being governed by the adrenal system, the main factors of the above respiratory process, the production of eosinophile cells and of adrenal secretion, are thus dependent upon the functional integrity of this system.

6. The neutrophile leucocytes which accompany the eosinophiles migrate from the capillaries of the pulmonary artery to the perialveolar lymphatics, and supply the interlobular structures with their nutritional and functional elements: i.e., peptones, myosinogen, and fibrinogen.

7. During certain diseases neutrophile and basophile leucocytes may also penetrate into the alveoli and be found in the sputum.

The Basophile Leucocytes.—These cells show the division into two groups, "finely-granular" and "coarsely-granular," which characterizes those just reviewed. They seem to differ from the latter in every other way, however, for, while these are amœboid, basophiles are not considered so by most histologists. Gulland—rightly, in our opinion—contends that they are, the variations of shape that they show and the manner in which they are scattered throughout the body being adduced as main reasons. The nucleus is round, oval, or kidney-like; is less clearly differentiated from the cell-substance; and stains with much greater difficulty than that of the neutrophile.

As regards their distribution, Ehrlich and Ranvier found them in the peritoneal, pleural, and pericardial cavities, and also in the connective tissue, but, as emphasized by Kanthack and Hardy, the cells in the connective tissue differ somewhat in shape and size from those in the three cavities mentioned. The latter investigators also found the coarsely-granular basophiles "exceedingly numerous in connective-tissue spaces, where they form sometimes an almost complete sheath for the *lymph*-capillaries." Their distribution furthermore resembles that of the eosinophiles in the fact that they are relatively very scarce in the blood.

The chemical characteristics of the basophile granules is suggested by a curious phenomenon which is especially noticeable in animals, and to which Kanthack and Hardy refer in the following words: "The unstable, or *explosive nature* of the coarsely-granular basophile cells in certain animals is one of their most remarkable characters. In the rat and mouse perfect preparations of these cells may be very easily made, but in the guinea-pig and rabbit they can be preserved only with the most rapid fixation by heat or absolute alcohol. In these animals the mere exposure of the cœlomic fluid to the air, or to contact with a cover-slip for a few seconds, is sufficient to cause their complete disappearance. Cells characterized by great instability have been described elsewhere in astacus[50] as the 'explosive' cell of that animal, and the basophile cells of

[50] Hardy: Journal of Physiology, Nos. 1 and 2, vol. xiii.

the guinea-pig and rabbit might, with equal justice, be designated the explosive cells of those animals." A familiar histological fact will suggest the relationship between such a cell and the oxidizing substance. Berdal,[51] quoting Ranvier, says: "The action of oxygen or of the air may be observed in an extremely simple way: A lymph preparation which has served for the examination of amœboid movements is carefully surrounded with paraffin and set aside for thirty-six hours. If, at the end of that time, the lymphatic cells are examined, all will be seen to have reassumed the spherical form and to no longer project pseudopodia. Removal of the paraffin and raising of the disk so as to admit a small quantity of air will suffice to cause the amœboid motion to recur." The explosive nature of the coarsely-granular basophile cell can only be due to the one cause: the presence of large proportion of phosphorus, both in its nuclein and granules.

In their paper upon the free granules derived from leucocytes Stokes and Wegefarth review the investigations of H. F. Müller, of Nothnagel's clinic.[52] This observer found them both in diseased and normal blood, and describes them as "highly refractive, round or dumb-bell shaped bodies, which show a dancing, molecular movement, but no independent motion." When mounted in 1-per-cent. osmic acid "the reaction for fat does not occur," nor can they be dissolved by acetic acid or ether. An important feature in connection with our inquiry is that Müller is recorded as stating that "he does not consider them as Ehrlich's neutrophilic granules escaped from leucocytes" and that "the neutrophilic granules are dissolved by dilute acetic acid, while the bodies which he has studied are not dissolved by this acid." This is in perfect accord with the chemical analyses of Milroy and Malcolm, who found that acids dissolved eosinophile granules, and with the observations of Lenhartz in respect to those found in sputum. Stokes and Wegefarth further emphasize the dissimilarity of basophiles from acidophiles in general, as viewed from our standpoint, when they say, doubtless referring to Ranvier's interpretation of the purpose of the granules of white globules: "They are

[51] Berdal: *Loc. cit.*, p. 275.

[52] H. F. Müller: Centralbl. für allg. Path. u. path. Anat., vol. viii, 1896.

not concerned in the formation of fibrin, since they remain outside of the fibrinous net-work or are only accidentally attached to it." We thus have evidence to the effect that basophiles are different from neutrophiles, both chemically and functionally.

What is the nature of these granules? Müller is stated to disbelieve "that they are true particles of fat, since they do not give a reaction with osmic acid," while he is credited with the opinion "that they may be bodies resembling fat, but which fail to show the osmic-acid stain." Indeed, the persistence with which this characteristic appearance is noted by investigators is noteworthy. Thus, Kölliker,[53] Ranvier,[54] Bizzorero,[55] von Lünbeck,[56] and Hayem[57] are referred to by Stokes and Wegefarth as having also observed bodies resembling fat-granules in the blood of normal human beings, those of the last-named investigator and others described by Schiefferdecker and Kossel[58] also as fat-granules being thought by Müller to be identical to those observed by him. That they are fat-*like*, as thought by Müller, but not fat, seems to us quite clear.

Müller, we have seen, refers (as do other investigators) to the fact that these granules are "highly refractive." As this sign also attends eosinophilic granules, it would appear to have but little differential value; such is not the case, however, when this property is jointly considered with the osmic-acid reaction, for we have here the *two main distinctive signs of myelin*. "It is extremely refringent," writes Berdal, referring to the latter; and he also alludes to the familiar fact that "myelin treated with osmic acid" stains black.

Still, if the granules are composed of myelin, the active constituent of the latter, lecithin, should be present, since we found this body not only in the myelin of nerves, but also in that of the neuron and the interior of the dendrites. That some granules do contain this body is evident, inasmuch as Foster, in his review of the physiological chemistry of white corpuscles, writes: "Next in importance to the proteids as con-

[53] Kölliker: "Handbuch der Gewebelehre des Menchen," 1867.
[54] Ranvier: "Traité Technique d'Histologie," 1875.
[55] Bizzorero: "Handbuch der klin. Med.," 1887.
[56] Von Lünbeck: "Grundriss einer klinischen Pathologie des Blutes," 1896.
[57] Hayem: "Du sang et de ses altérations anatcmiques," 1889.
[58] Schiefferdecker and Kossel: Gewebelehre, Bd. xi, 1891.

stant constituents of the white cells come certain fats. Among these the most conspicuous is the complex fatty body, *lecithin.*" As we now know that the nuclei of all leucocytes are similar in composition, this can only apply to their granules.

This involves the necessity of differentiating between the two kinds of granules present, the acidophiles (neutrophiles and eosinophiles) and basophiles. Professor Foster points to this distinction, it seems to us, when he says: "next in importance to the proteids, etc." The basophilic granules are evidently not composed of nucleo-proteids: a fact which eliminates the acidophile cells and their granules. Indeed, we have confirmatory evidence that it is not the latter which contain lecithin in the following allusion to both kinds of acidophile granules by Milroy and Malcolm: "The fact that neither alcohol nor ether dissolves the granules excludes the possibility that they consist of fat or lecithin."

How do basophile cells acquire their lecithin-building constituents? As is well known, emulsified fats also penetrate the intestinal villi, but, instead of entering as do nucleo-proteids into the venules, they enter the lymphatic circulation directly, by way of the lacteals. Are they absorbed by the villi, and then by the lacteals, or are they also taken up by leucocytes and carried into the latter? Inasmuch as the lymph contained in the lymphatic vessels is itself crowded with leucocytes similar to some of those found in the blood-stream, we must first ascertain whether these leucocytes in any way leave the lymphatic circulation in the intestine as they evidently do when the lymph-ducts open into the general venous system at the junction of the internal jugular and the subclavian veins on both sides.

It may prove useful, however, to first recall the fact that the so-called "chyme" and "chyle" represent the same liquid, *i.e.*, the lymph, and that these terms were suggested by a temporary *quantitative* difference in the constituents of the lymph in the mesenteric lymphatics, which are greatly increased during the process of absorption. Again, it may also be well to refer to the fact that lymph is merely blood-plasma practically devoid of red corpuscles, but containing lymphocytes and coarsely-granular basophile leucocytes, and, besides, minute fat-

globules which show an active Brownian movement, though covered with a thin layer of protoplasm to prevent their running together as fat-drops are wont to do.

"Lymph also contains fibrin," writes Professor Duval, "but a fibrin which is slow to coagulate spontaneously; indeed, lymph removed from the vessel begins, after a quarter of an hour or so, to harden into a colorless jelly, from which a reticulated mass soon becomes separated as does blood-fibrin undergoing coagulation." The cause of this delay seems to us but a natural result of the absence of both varieties of acidophile leucocytes, while the slow coagulation is but a normal consequence of the fact that the lymph is plasma which, though derived from the blood, and deprived of neutrophile leucocytes, nevertheless contains more or less fibrinogen. "More or less" is applicable in a double sense here, for lymph taken from the lymphatics of the extremities, for instance, coagulates more rapidly than that taken from some vessels of the trunk. Lymph also contains serum-albumin and serum-globulin in reduced quantity, and relatively very small proportions of urea, neutral fats, and sugar, as compared to the blood. Such is not the case, however, as regards inorganic salts, which are present in the lymph and blood in similar proportions.

What is the nature of the process through which fats are taken up from the intestine and their itinerary in the blood-stream until they are used for the elaboration of basophile granules?

Stewart,[59] referring to the nature of this process, says: "The common view has long been that the greater part of the fat escapes decomposition, and, after emulsification by the soaps formed from the liberated fatty acids, is absorbed as neutral fat by the epithelial cells covering the villi. If an animal is killed during digestion of a fatty meal, these cells are found to contain globules of different sizes, which stain black with osmic acid, and dissolved out by ether, leaving vacuoles in the cell-substance, and are therefore fat. It has always been difficult to explain how droplets of emulsified fat could get into the interior of the epithelial cells, and yet it certainly passes

[59] Stewart: *Loc. cit.*, p. 370.

into them, and not between them." Foster also refers to this feature in the following quotations: "It has, it is true, been maintained by some that they [the neutral fats] pass *between*[60] the cells, and not into them, but the evidence is distinctly against this view." Alluding to the rods of the striated border, he says: "We may imagine that the globules pass into the cell-substance by help, in some way, of these rods through amœboid movements comparable with the ingestive movements of the body of an amœba; but we have no positive evidence to support this view." . . . "Within the columnar cell, the fat may be seen, both in osmic-acid preparations and in fresh living cells, to be disposed in globules of various sizes, some large and some small, each globule placed in a space of the protoplasmic cell-substance. It does not follow that the fat actually entered the cell exactly in the form of these *globules;* it may be that the fat passes the striated border in *very* minute spherules, which, reaching the body of the cell, run together into larger globules; but whether this is so or not we do not know."

All this seems to pointedly suggest that the epithelial cells take up minute fat-particles to submit them to some local process. Böhm and von Davidoff[61] emphasize the feature of the process when they say, referring to the fat-globules in the epithelial cells: "It seemed most probable that protoplasmic threads (pseudopodia) were thrown out from each through its *cuticular* zone, which, after taking up the fat, withdrew with it again into the cell. But when it was shown that, after feeding with fatty acids or soaps, globules of fats still appeared in the epithelial cells as before, and that the chyle also contained fat, the hypothesis was suggested that the fat is split up by the pancreatic juice into glycerin and fatty acids, and that the fatty acids are then dissolved by the bile and the alkalies of the intestinal juice only again to combine with the glycerin to form fat *within* the epithelial cells." Stewart further states that "when an animal is fed with fatty acids they are not only absorbed, but appear as neutral fats in the chyle of the thoracic duct, having combined with glycerin in the intestinal wall, and the epithelial cells contain globules of fat, just as they

[60] All italics below this word are our own.

[61] Böhm and von Davidoff: *Loc. cit.*, p. 256.

do when the animal is fed with neutral fat." It seems clear, from these and other available data, that *the epithelial cells of the villi capture fat-globules from the intestinal contents and if need be convert this fat into neutral fats.*

We have seen, however, that the villi also take up the leucocytes which ingest proteids. It is important, in this connection, to clearly distinguish the two mechanisms involved one from the other. Böhm and von Davidoff testify to the passage of such cells into the villi by stating: "Leucocytes are sometimes found within the epithelial cells, but more usually between them, and, according to Stöhr, when seen in these positions are in *the act* of migrating into the lumen of the intestine." Stewart, however, remarks, in this connection: "Leucocytes have been asserted to be the active agents in the absorption of fats. They have been described as pushing their way *between* the epithelial cells, fishing, as it were, for fatty particles in the juices of the intestine, and then traveling back to discharge their cargo into the lymph. This view, however, is erroneous." It is erroneous, but only in one respect, in our opinion, *i.e.*, their direct connection with the absorption of fats, for, as stated, the functions of these wandering cells is to carry proteids to the intravillous venules. These do not, therefore, enter the intravillous lacteals. But *other* leucocytes penetrate the latter with the neutral fat-globules. "Although the leucocytes do not aid in the absorption of fat from the *intestine,*" says Stewart, "they appear to take it up from the epithelial cells, conveying it through the spaces of the net-work of adenoid tissue that occupies the interior of the villus, to discharge it into the central lacteal, where it mingles with the lymph." The distinction we suggest in this connection appears to us to remove the confusion that exists in the literature of the subject. Briefly, our conception of the process is as follows: *While the leucocytes which ingest proteids from the intestinal foodstuffs pass between the epithelial cells and enter the venules, the leucocytes which ingest fats only carry the latter from the inner limits of the epithelial cells to the interior of the lacteal, and deposit them therein.*

Professor Foster expresses the opinion that the number of leucocytes found to contain any appreciable degree of fat is

too small to account for the amount of fat absorbed. But it seems to us that, if these only transfer the fat from the epithelial cells to the lacteals, the to-and-fro excursions of each cell and the enormous number of villi over which the food of a single meal has to pass amply compensate for the apparent paucity of cells. An additional reason adduced by Professor Foster is the fact that the administration of a saline such as magnesium sulphate "produces effects the very reverse of absorption," these cells being present in unusual numbers. As interpreted from our standpoint, and as will be shown when the action of purgatives is studied, these agents greatly increase the flow of serum into the intestinal canal by reflex action and crowd its walls with defensive agencies, including leucocytes. We are dealing here, not with a normal process, such as is the fat-absorbing function, but with an engorgement by protective elements.

The axial contraction and relaxation which occurs in the villus to cause its various contents to gravitate into their respective channels may, however, be instrumental in causing fat-particles that have already passed the epithelium to enter, not only the lacteal, but the venules also, fat-globules, or what purported to be such, having been found in the blood. This feature, and the manner in which fat-globules reach the general lymphatic circulation, are exemplified in the following lines by Stewart: "The contraction of the smooth muscular fibers of the villus and the peristaltic movements of the intestinal walls alter the capacity of the lacteal chamber, and so alternately fill it from the lymph of the adenoid reticulum and empty it into the lymphatic vessel with which it is connected. By this kind of pumping action the passage of fat and other substances into the lymphatics is aided. In the dog no fat is absorbed by the blood-vessels, except perhaps a small quantity in the form of soaps; it nearly all goes into the lacteals, and thence by the general lymph-stream through the thoracic duct into the blood."

An interesting feature now asserts itself. Again are all the basophiles poured into a channel, the left subclavian vein, which empties into a large venous trunk, the superior vena cava, which in turn carries them to the right heart. We have

practically a repetition of the process witnessed in the case of the neutrophiles with the exception of the passage through the liver, the basophiles being directly transmitted to the heart, and therefore likewise to the pulmonary lobules.

Indeed, we find our view that the granules of these cells *are* myelin amply confirmed in this connection, for, while Lenhartz alludes to the neutrophilic granules found in colorless sputum, and to the fact that the sputum of asthmatics contains "numerous eosinophile and quite numerous *basophile* leucocytes," he also refers, when reviewing the characteristics of the cells observed microscopically in this connection, to cells that "present considerable coarse granulation," and remarks: "Here, however, the spherules show a decidedly dull appearance, resembling that seen in *crushed nerve-substances.* For this reason they were designated by Virchow as *myelin droplets.*" Moreover, Lenhartz[62] publishes a colored plate, one of the figures of which represents what he terms with E. Wagner "heart-lesion cells" found in the lungs. The granules of these, he says, "are similar to myelin, and, occasionally, *more refringent than fat.*"

Evidently the nervous system is supplied with its myelin precisely as the muscles are supplied with their myosinogen. Kanthack and Hardy state that the coarsely-granular cells are not only rare, but completely absent from the blood, while the finely-granular are relatively rare in the latter except some hours after a meal. "To say that these cells are found in the body only in very small numbers, being confined to the blood and scanty even there," remark these investigators, referring to the finely-granular basophiles, "is probably only equivalent to saying that we are at present very ignorant as to their history, distribution, and significance. However, since we find this cell in the blood, but do not find it either in the cœlomic fluid or in the interstitial spaces of the tissues (except, perhaps, in those of the mucous coat of the *alimentary canal*), we must, until further facts are forthcoming, regard it as the basophile cell of the blood." Still, they refer to the coarsely-granular cells as "occurring only in the extravascular spaces" and in the "interstices of the connective tissue."

[62] Lenhartz: "Mikroskopie und Chemie am Krankenbett," 1900.

It seems to us that we have in the finely-granular cell the freshly-laden cell on its way, when in the blood, to its normal habitat, the connective-tissue spaces, where their granules develop into their normal size. Indeed, Gulland alludes to a basophile cell, represented in one of his plates, of which he says: "The leucocyte was seen to have been fixed in the act of *passing through a narrow hole* between two bundles of connective tissue." This cell is furthermore accompanied by a large number of granules held in a net-work of fibers, which the cell appears to drag along in its travels. It is of this variety of leucocyte that Gulland says: "It has often been remarked that these cells show a great tendency to leave their granules behind them," etc., and the one which, in the portion of this section devoted to a review of the general properties of leucocytes, stands pre-eminently as a free-granule producer.

That the cell in migrating from the vessels and passing through connective-tissue interstices has for its purpose to reach the myelin spaces of nerves is clearly suggested by the manner in which the lymphatic spaces are arranged even in the finer ramifications. "In its course Henle's sheath is not applied against the nerve-tube," writes Berdal[63]; "there is between it and the nerve-tube a space occupied by lymph-plasma which has for its purpose to supply the cylinder-axis with its nutrition." If this statement is interpreted from the standpoint of our views, it is more than nutrition, but myelin-granules, which insinuate themselves—through chemical affinity, doubtless—wherever there is need for them: *i.e.*, wherever their consumption has been greatest. "Medullated nerve-fibers, when examined, frequently present a beaded or varicose appearance," say Pick and Howden[64]; "this is due to manipulation and pressure causing the *oily* matter to collect into drops, and in consequence of the extreme delicacy of the primitive sheath even slight pressure will cause the transudation of fatty matter, which collects in drops of *oil* outside the membrane." Evidently we are not dealing with a fixed mass, but with one made up of extremely mobile particles, which to us, at least, represent as many basophile granules. If the space between Henle's sheath

[63] Berdal: *Loc. cit.*, p. 152.
[64] Pick and Howden: *Loc. cit.*, p. 1117.

contains lymph supplied with myelin-granules, what is the difference between a nerve thus supplied with its primary source of energy and a "medullated" nerve? None, it seems to us. *Such a nerve as a non-medullated nerve does not exist,* therefore; since a nerve deprived of myelin, if interpreted from our standpoint, would become a mere plasma-channel.

The pathway to all nerves becomes greatly simplified down to their terminal ramifications, it seems to us, in the presence of Gulland's observation concerning the passage of a basophile leucocyte "through a narrow hole between two bundles of connective tissue." Indeed "the lymphatic vessels do not exist as distinct channels in the interfascicular connective tissue," says Berdal. "There is no lymphatic vessel in the thickness of the nervous bundles nor in the sheath surrounding them (Ranvier). The circulation of the lymph, in the interior of the bundles, is insured by the arrangement of the interfascicular connective tissue, the meshes of which represent lymphatic cavities communicating with the vessels of the interfascicular tissue through *holes* in the lamellar sheaths." On the whole, therefore, it seems to us permissible to conclude that:—

1. The physiological function of the basophile leucocyte is to convert fats derived from the intestinal foodstuffs into myelin-granules, and to distribute the latter to all parts of the nervous system, including the brain.

2. The basophile leucocytes thus supply the entire nervous system with the lecithin-containing compound which combines with the oxidizing substance of the blood-plasma of axis-cylinders, neuroglia fibrils, etc., in the production of nervous energy.

Leucocytes and their Relations to Vital and Functional Processes.—The varieties of leucocytes reviewed represent, it seems to us, the only three adult functional types, the lymphocytes and hyalines being, as stated, immature cells. This does not mean, however, that the latter are functionless; indeed, we have seen that when an active process is initiated these younger cells rapidly increase in the blood and intestinal tract to replace the large number of their elders that have disappeared to take part in this process. Their development must be extremely rapid, therefore, and their number commensurate with the number of adult leucocytes brought into action,

whether this be to distribute (1) the neutrophilic peptones, myosinogen and fibrinogen granules; (2) the eosinophilic hæmoglobin granules; or (3) the basophilic myelin granules.

On page 668 we said: "The closer is the intimate nature of the leucocyte examined, the more does it become evident that this cell must be endowed with functions greatly exceeding in importance any as yet ascribed to it." The results of our analysis seem to us to have fully sustained this assertion. Indeed, if the functions subserved by these cells are enumerated, it will be found that *they supply the entire organism with the agencies which combine with the oxidizing substance to insure the continuation of life and the efficiency of all organic functions.*

THE FUNCTIONS OF LEUCOCYTES IN IMMUNITY.

In the preceding chapter we ventured the opinion that Ehrlich's side-chain theory did not, in its present form, account for the protective phenomena witnessed in the organism, and that the solution of the problem required research in other directions. The complexity of this hypothetical process; the need of specific toxophoric atoms to counteract as many specific toxins; the implied necessity of an antenatal arrangement of the molecular elements of the cells, with adjustment to the requirements of existence in disease-ridden communities; Ehrlich's own investigations showing that immunity is not transferred to progeny through the germinal cell, etc., were adduced as fundamental reasons for the position taken. What work we have done since has but emphasized these objections, especially as regards the multiplicity of antitoxins, cytolysins, and haptophore groups. But it has also brought to light, it seems to us, those features of his invaluable researches which are beyond the domain of pure conjecture.

Professor Welch, in his masterly Harvey Lecture, quotes Behring's terse definition of Ehrlich's theory: *i.e.*, "The same substance which, when incorporated in the cells of the living body, is the prerequisite and condition for an intoxication, becomes the means of cure when it exists in the circulating blood." As, in the light of our own views, the cell involved is a leucocyte, the prophylactic function would thus be exercised by granules formed mainly of products of digestion. If the foods in-

gested by this cell included bacteria, these would become, therefore, the source of the bactericidal granules, according to Ehrlich's theory. That such is not the case we have seen.

To the question: "What is the physiological mechanism called into action in the processes resulting in the production of antitoxins, cytolysins, and similar bodies?" Ehrlich is stated by Welch, however, to answer: "The mechanism is one physiologically employed for the assimilation by the cells of food. The receptors are in the cells, not for the purpose of linking poisons to the cells, but to seize certain foodstuffs, particularly the proteids, and the toxins and bacterial and other foreign cellular substances, if capable of inducing the immunizing reaction, chance to have the requisite combining affinities for the food-receptors." There is obviously considerable analogy between this and our own interpretation, although the latter is devoid of the complex questions introduced by specific affinities. The cellular trypsin seems to us to be endowed with all the bactericidal and toxin-destroying power required. Indeed, trypsins appear to us to embody the functions attributed to all the complements: Buchner's alexin, and Metchnikoff's cytase, while the oxidizing substance corresponds with Ehrlich's amboceptor: *i.e.*, Bordet's sensitizing substance, or fixative.

We are also vividly reminded of the fluctuations of adrenal activity by the following words of Professor Welch's: "We know that the content of the blood in specific anti-bodies, and especially in complements, varies in significant ways under diverse conditions, as in infancy and in adult life, in health, in different states of nutrition, under the influence of fatigue, of inanition, of pain, of interference with respiration, of alcohol, and in disease."

We likewise find confirmation of the view we have submitted as to the causes of the vulnerability of children to infectious diseases: *i.e.*, inadequate protection through lack of adrenal development, in the following lines by the same author: "The infant comes into the world with protective anti-bodies in the blood smaller in amount and less energetic than those possessed by the healthy adult. It is an important function of the mother to transfer to the suckling through her milk immunizing bodies, and the infant's stomach has the capacity,

which is afterward lost, of absorbing these substances in an active state. The relative richness of the suckling's blood in protective anti-bodies, as contrasted with the artificially fed infant, explains the greater freedom of the former from infectious diseases." Evidently the importance we have attached to the immunizing constituents of the mother's milk was not groundless. What a holocaust of lives to be charged to the so-called infant-foods!

Finally, the general protective process as we have conceived it seems to us sustained. We have suggested that accumulation in the blood of toxic waste-products occurred when, owing to advanced insufficiency of the adrenals, the oxidizing substance was inadequately formed. Obviously, the reduction of all oxidation processes *inhibits leucocytogenesis* and the splenopancreatic functions, and, as a result, bacteria, their toxins, toxic waste-products, etc., are no longer antagonized. "One of the earliest results of the systematic bacteriological examinations which we make at all necropsies at the Johns Hopkins Hospital," writes Professor Welch, "was the recognition of the great frequency of terminal infections, formerly often undetected by the clinician, in chronic diseases, particularly of the heart, the blood-vessels, and the kidneys. Dr. Longcope finds, although not regularly, still in many cases of these diseases, a marked reduction in the quantity of complements, which may amount to a total loss of the colon complements. The analysis of the cases brings out unmistakably a definite relation between this loss of complement and the predisposition to infection."

If the full meaning of these few quotations is grasped, it will become apparent that the newer conceptions we have incorporated in this work are vividly reflected in the modern contributions to our knowledge of immunity.

The adrenal system, as suggested by the foregoing quotations, stands out prominently in all problems concerned with immunity. The oxidizing substance may be said, therefore, to occupy the same relative position.

Bordet in a series of exhaustive experiments[65] ascertained that the destruction of bacteria was due to the action of two

[65] Bordet: Annales de l'Institut Pasteur, vol. ix, 1895, and vol. x, 1896.

substances: (1) Buchner's alexin, a product of leucocytes; (2) a body which, though present in small quantities in the plasma during health, *i.e.*, under normal conditions, was found to greatly increase in quantity in infected animals. Referring to these investigations, and to those of Pfeiffer, reviewed in our eleventh chapter, Metchnikoff[66] writes: "The researches of M. Bordet[67] have definitely elucidated this question. This scientist has demonstrated that Pfeiffer's phenomenon is produced by all sera with the aid of the same substances, which are the *cytases* (alexin, or Ehrlich's complement). But *in the serum of vaccinated animals* there is *added* to them the fixative (the substance sensibilisatrice of Bordet or immunizing body, Ehrlich's amboceptor), which itself shows *specific properties.* After having well distinguished one from the other, the two substances that intervene in the granular transformation of vibrios, M. Bordet has proven that in vaccinated animals it is the *fixative which increases in quantity,* while the cytase (alexin) remains as to quantity in about the same proportion as that observed in normal animals." . . . "While the cytase does not increase as the result of vaccinal injections, the fixative, on the contrary, becomes more and more abundant. It is this second soluble ferment which imposes its characteristic upon the blood-stream."

If this fixative, amboceptor, intermediary body, etc., is the oxidizing substance, are we justified in granting it a position in immunity overtopping that of all other agencies? In other words, does Buchner's alexin, Ehrlich's complement, Metchnikoff's cytase, etc., play as insignificant a rôle as the experiments referred to suggest?

We have furnished evidence to the effect that the bactericidal phagocytes, the neutrophiles, absorbed trypsin (the spleno-pancreatic secretion) not only in the intestinal canal, but likewise in the portal vein. To this secretion we ascribed the destruction of all toxic albuminoids, toxins, vegetable poisons, venoms, etc. Bacteria being likewise ingested, they naturally find their doom in the digestive vacuoles of the phagocytic neutrophiles, through the effects upon them of the

[66] Metchnikoff: L'Immunité dans les Maladies Infectieuses," p. 204, 1901.
[67] M. Bordet: Annales de l'Institut Pasteur, vol. ix, p. 462, 1895.

trypsin absorbed by the latter. "Just as amœbæ digest their prey with the aid of amibodiastase, a soluble ferment belonging to the group of *trypsins*," writes Metchnikoff,[68] "white corpuscles submit the foreign bodies they inglobe to the action of cytases. These cytases (the alexins or complements of other authors) are the soluble ferments which also belong to the category of trypsins." It is necessary to bear in mind, however, that the physiological rôle of the neutrophile as we have conceived it is foreign to immunity, *i.e.*, to the production of myosinogen and fibrinogen, and that what trypsin penetrates into this cell acts only under *normal* conditions as a digestant upon the bacilli, and is not, therefore, eliminated as such by the cell. It seems evident, therefore, that Metchnikoff is right when, as stated by Welch, he "strenuously insists . . . that the complement or cytase is within the leucocytes, from which it is not secreted." Still, this does not give us the clue to the manner in which the general blood-stream is supplied with protective toxin-destroying bodies.

The neutrophiles, which represent three-fourths of all white cells found in the blood, appear as the normal agents for this purpose; but how reconcile the fact emphasized by Metchnikoff that his trypsin-laden cytase does not leave these cells? This is perhaps explained by another quotation from his text[69]: *i.e.*, "The cytases must be classed among soluble ferments which do not leave the phagocytes while these remain intact. But as soon as these cells are injured they allow a portion of their cytases to escape from their contents." If this is the only process through which the blood is supplied with its trypsin, we are led to the deduction that in all intoxications due to albuminoid bodies injury to neutrophiles is necessary: an inapplicable mechanism in the general blood-stream when general infections are present. Indeed, we have not been able to find in this distinguished zoologist's work evidence that the phagocytes at any time part with their cytase for the purpose of distributing it throughout the organism. He only refers to the elimination of the trypsin-containing substance as passing out of the cells *after* these have been taken from the organism: *i.e., extra*

[68] Metchnikoff: *Loc. cit.*, p. 573.
[69] *Ibid.*

corpore. Thus, he remarks (incidentally, though indirectly, confirming our view that neutrophiles are the source of fibrinogen granules): "In blood *removed from* the *body* the white cells allow *plasmane,* which *causes* coagulation of fibrin and the formation of the clot, to pass into the liquid. But at the same time these cells abandon a portion of their cytase, which communicates to the serum its hæmolytic and bactericidal qualities." In the body, however, the need of injury to liberate the cytase, and the stated fact that this trypsin-laden body (alexin) is strictly intracellular, represent the features of the question that are especially emphasized by Metchnikoff.

This is accounted for by an important feature of this investigator's views: *i.e.,* he regards the intermediary substance, Bordet's fixative, Ehrlich's amboceptor (our oxidizing substance), as a product of these cells, as shown by the following lines: "The cytases are essentially intracellular soluble ferments; the fixatives are, on the contrary, true humoral soluble ferments. But, though circulating in the plasma, the fixatives are unquestionably of cellular origin. This fact was first shown by Pfeiffer and Marx, who found the specific fixative of cholera vibrios in the 'hæmatopoietic organs,' that is to say, the spleen, the lymphatic ganglia, and the bone-marrow at a period when none were present in the blood."

We have shown the direct functional relationship between the adrenal system and leucocytosis. That the oxidizing substance, which invades the entire blood-stream in increased quantity under the influence of a toxic, should have reached the structures mentioned at an early stage of the morbid process is quite plain. Indeed, the proof adduced by Metchnikoff is easily accounted for without in any way attributing to the leucocytes themselves the production of the fixative. We have seen, for instance, that the splenic artery, as a branch of the cœliac axis, is one of the first to receive freshly oxygenized blood; the lymphatic system, which has a serum-containing capacity twice that of the entire blood-system, receives fresh serum from the pulmonary lymphatics, etc., before it even has time to penetrate the blood, etc. Again, none of the leucocytes we have studied afford a single physical or chemical feature tending to suggest that the fixative is a product of these cells.

We must frankly claim, on the other hand, that its production —as oxidizing substance—through the intermediary of the adrenal system has been supported in this entire work by a wealth of evidence seldom equaled in the annals of medicine when an entirely new line of thought was being submitted for the first time.

The oxidizing substance has affirmed its identity on all sides as the reagent which, by combining with products, so to say, stored in the cellular elements—through the agency of the leucocytes—causes the liberation of functional energy. Wherever in the organism we witness vital or functional phenomena, these must be accounted for by a reaction in which the oxidizing substance takes part. To insure the liberation of this energy in the organism itself, the presence of the two sources of energy are necessary for the reaction. When blood is removed from the body, therefore, it is only when both are present that bacteria, red blood-corpuscles, etc., can be chemically disintegrated. The multitude of contradictory phenomena connected with experimental germ- and blood-cell- destruction recorded in literature seem to us to find their explanation in the fact that this *fundamental feature* of the processes involved has been totally overlooked.

Metchnikoff, as just stated, found that in blood removed from the body, the leucocytes allow what he terms "plasmane" (because it coagulates fibrin, he thinks) to pass into the liquid. "At the same time," he asserts, "these cells abandon a portion of their cytase, which communicates to the serum its hæmolytic and bactericidal qualities." It is evident that M. Metchnikoff considers plasmane as the *cause* of coagulation of fibrin, whereas we consider the cells as the source of the agent which becomes coagulated by what remains of oxidizing substance in the extravasated blood. In other words, what M. Metchnikoff deems the causative factor of coagulation is a substance which he regards as a product of the cell, whereas we consider this cellular product as the one acted upon by an agency in the plasma. Of course, coagulation in one sense is due to the *ultimate* absence of oxidizing substance, because its existence as fibrin is due to the fact that it is not completely consumed by the oxygen. But to become coagulated at all it requires the

momentary exposure to the action of the oxidizing substance. A sudden arrest of the supply of the latter to the blood, as occurs when a large dose of venom causes the functions of the adrenal system to cease, for example, accounts for the liquid blood witnessed under such circumstances. The tissues, continuing the consumption of oxygen, soon deplete the blood of this gas, leaving none to carry on the *partial* oxidation of the fibrinogen to which the formation of fibrin is due. We have evidence here, therefore, through the fact alluded to by Metchnikoff, that coagulation occurs in the extravasated blood, of the presence in it of at least a small quantity of oxidizing substance. As we view the composition of this extravasated blood, therefore, it embodies (1) fibrinogen, (2) the oxidizing substance, and (3) the cytase, including its trypsin, as factors of the process through which bacteria and blood-cells are disintegrated.

An application of the principles we have submitted will serve to illustrate our meaning. Referring to the labors of Bordet, Metchnikoff[70] states that "whenever the serum of a prepared animal is deprived of its hæmolytic properties by heating to 55° or 56° C., this property can be restored to it with certainty by adding to it a little *normal* serum incapable itself of causing hæmolysis. The heated serum of prepared animals completely loses its power of dissolving its red corpuscles, but it *preserves* its other acquired property of *agglutinating* the latter. The red corpuscles in voluminous masses visible with the naked eye remain intact indefinitely if allowed to remain in the prepared and heated serum. But if a small proportion of *normal* blood (obtained from many species of vertebrates) is added, dissolution of the corpuscles soon follows. There is initiated under these conditions a process in which two substances take part, one of which was present in the heated serum of the prepared animal, and the other in the non-heated normal serum. The first of these substances which resists not only the temperature of 55° to 56° C., but stands, without undergoing alteration, heating up to 60° to 65° C. corresponds with the intermediary substance of M. Ehrlich [our oxidizing substance].

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[70] Metchnikoff: *Loc. cit.*, p. 97.

It has been designated by M. Bordet under the name of 'sensitizing substance' [fixative]. The second insignificant [*'banale'*] substance, that found in normal sera, is the alexin of Buchner and Bordet, or Ehrlich's complement."

What is the active cytolytic constituent of the normal serum? A material difference between Buchner's alexins and Bordet's fixative, that is to say, between the trypsin-laden cytase and the oxidizing substance, is the fact, recognized by all, that the alexin, or cytase, is destroyed when exposed to a temperature of about 56° C., while the fixative, or oxidizing substance, can stand without harm a temperature of about 65° C. It becomes evident, therefore, that the agency disabled "by heating to 55° to 56° C.," referred to by Metchnikoff, must have been the alexin. But how did the addition of "a little normal serum *incapable itself of causing hæmolysis*" restore the serum's hæmolytic powers? It is clear that there must have been something in the latter with which it could combine to bring about the reaction necessary for the liberation of functional energy to which we have referred. And what is the nature of this required agency? The second portion of the quotation furnishes a clue to its identity: *i.e.*, the fact that, while losing its power of dissolving red corpuscles, the serum of a prepared or infected animal preserves its property of agglutinating the latter. Indeed, this agglutination points to the presence of fibrin, which, as interpreted from our standpoint, is a *phosphorus*-laden body. But, then, *how* did hæmolysis occur when the normal serum was added? The fibrin on being exposed to the action of the oxidizing substance could only have liberated the agglutinated blood-corpuscles by causing dissolution of the fibrinous filaments, and without affecting the red cells. The process evidently requires another agency: a body which only becomes active in the blood when aided by the energy liberated by the combination of fibrinogen and oxidizing substance.

Again, "M. Bordet has shown," writes Metchnikoff, "that the serum of animals injected at various times with the blood of foreign species contains almost the same quantity of alexin as does normal serum. But, on the other hand, it is the sensitizing substance [the fixative, oxidizing substance, etc.] which

appears in very great quantity as a result of these injections. M. de Dugern[71] has confirmed this observation, and has added the interesting fact that the sensitizing substance is found in great excess in the serum of prepared animals. When *fresh, non-heated* blood is added to this serum, the hæmolysis produced is thirty times more active than occurs with the serum of the prepared animal alone." How could hæmolysis be increased thirty times simply by adding the *sensitizing* substance,—our oxidizing substance,—"which," using Metchnikoff's words, "fixes itself to the red corpuscle without ever dissolving it," a feature which, he adds, "is accepted by everyone and may be regarded as definitely settled"? In the light of our statements regarding fibrinogen, this body cannot be considered as the hæmolytic agent, since the blood-cells remained intact when in the first experiment they had been set free by the addition of fresh serum. In the latter experiment, however, the presence of alexin, the trypsin-containing body, is alluded to, even though supposed to be present only in normal quantities. This suggests that this trypsin may have played a rôle in the process not only in this, but likewise in the former experiment.

This is further sustained by the need of an agglutinating agent, for we have seen that, although heating caused the serum of an injected animal to lose its corpuscle-destroying character, its agglutinating power remained. We know the peculiar manner in which trypsin attacks albuminoids; it does not disintegrate them as do some other bodies by abstracting one or more of their constituents; it fairly corrodes the substances vulnerable to it, first melting corners, edges, etc., and softening the surface until the entire fragment has disappeared as would a gum-drop in water. Agglutination seems a normal outcome of such changes. Under these circumstances, however, trypsin cannot, as an agglutinant, be considered as a part of the alexin destroyed by heating to 55° C. or thereabouts, and must have, in the foregoing experiments, been liberated from the alexin by the heating process, thus being free to act when fibrinogen and oxidizing substance were present. In other words, it must also have been able to stand without harm the higher tempera-

[71] M. de Dugern: Münchener med. Wochenschrift, No. 20, p. 677, 1900.

ture—at least that of the oxidizing substance. Evidence of this is fortunately available. "It was supposed that the sensitizing or intermediary substance was likewise the substance which produced agglutination of the red corpuscles," writes Metchnikoff,[72] "but searching investigations have thoroughly established the difference between these two substances, which have as a common characteristic the fact that they both resist heating at 55° to 60° C. and beyond." Evidently trypsin is not only the agglutinating agency, but likewise that which destroys red corpuscles, bacteria, toxins, etc.

But if, as stated by Bordet, the alexin is not increased in the serum of periodically injected animals and it is only the sensitizing substance, our oxidizing substance, which appears in "very great quantity," how can we account for the thirty-fold hæmolytic power noted by de Dugern? It seems plain that a relatively small quantity of trypsin should be quickly disposed of under such circumstances, the hæmolytic process ceasing with corresponding promptness. But the fact that alexin can so easily part with its trypsin as suggested by the first experiments reviewed, on the one hand, and the correspondence between the temperature resistances of trypsin and the oxidizing substance, on the other, point to the fact that the *alexin* ratio of a serum may not in the least represent that of the trypsin ratio. The blood of the injected animal may thus have contained an ample supply to account for the great increase of hæmolytic power without showing an increase of alexin.

Indeed, we must not, in all this, lose sight of the fact that the conditions that prevail in extravasated blood do not portray conditions as they exist in living blood, and that such experiments can only be of value if, as in those referred to in the foregoing pages, all the elements introduced by the separation of the specimen from the *intra corpore* blood are taken into account. Thus, Martin and Cherry,[73] of Melbourne, refer to experiments by Calmette[74] which led him to conclude that "the toxin of snake-venom does not interact with its antitoxin *in vitro,* but only *in corpore,* and, therefore, that its action cannot

[72] Metchnikoff: *Loc. cit.*, p. 98.
[73] Martin and Cherry: British Medical Journal, Oct. 15, 1898.
[74] Calmette: Annales de l'Institut Pasteur, p. 250, 1895.

be explained as a simple chemical operation between the two." A similar observation is credited to Wassermann[75] in respect to the bacillus pyocyaneus. Metchnikoff's statement that in extravasated blood the leucocytes allow their "plasmane" and a part of their cytases, "which," he says, "communicate to the serum its hæmolytic and bactericidal qualities," to escape, therefore, is not applicable to the living blood-stream. Indeed, he emphatically asserts, as we have seen, that the cytase, the trypsin-containing body, exists under normal conditions solely within the leucocytes. The blood-stream, therefore, must find itself deprived of trypsin: the body which we have seen plays the primary rôle in the destruction of toxins and other toxic albuminoids. Still, this statement must be qualified.

We have seen, when the spleen and pancreas were analyzed, that the internal secretion of these organs was poured into the blood-stream about four hours after meals. Between-times its presence could hardly be detected experimentally. Again, post-prandial leucocytosis is a close companion of spleno-pancreatic functions; it also appears some time after a meal. The direct connection between the two is emphasized by the best possible proof: the presence, within the leucocyte, of the spleno-pancreatic secretion: *i.e.*, trypsin. The marked leucocytosis—of neutrophiles only as regards the blood-stream—that occurs after acute infections has been sufficiently emphasized. The question to determine is whether this secretion, which is poured into the portal vein by the splenic vein, is entirely absorbed by the leucocytes that pass the splenic veins' orifice when in the portal vein, or whether some is allowed to pass into the blood-stream.

The experimental evidence adduced in the preceding pages clearly illustrates the baneful results of free trypsin in the presence of the oxidizing substance and fibrinogen. As soon as these three agents are together, their destructive effects can even, we have seen, destroy red blood-corpuscles under appropriate conditions. The hepatic capillaries receive fresh arterial blood through the hepatic arteries, which arterial blood is mixed with the portal blood in the minute channels of the

[75] Wassermann: Zeitschrift für Hygiene, Bd. xxii, p. 521, 1896.

hepatic cells. We therefore have, in the latter, oxidizing substance and fibrinogen in active reaction: a fact demonstrated by the elevated temperature of the organ's parenchyma: *i.e.*, 106° F. That the delicate protoplasmic structures of the hepatic cells would be exposed to destruction were any considerable amount of free trypsin present in the blood seems obvious. Still, it is evident that a certain amount must be allowed to penetrate the organ to assist therein in the destruction of albuminoid toxics that have reached it through the digestive canal. When we consider the enormous number of channels which the liver contains, it is probable that considerable trypsin is distributed to this organ in a free state. Beyond the liver, however, and under normal conditions, analysis of the question again supports Metchnikoff, when he states that the trypsin-laden alexin is inclosed within the precincts of the leucocyte. But we must now lay stress upon the fact that this only applies to *normal conditions*, for, as soon as *abnormal* conditions prevail, another order of things is inaugurated.

Heat we have seen is the predominating factor of the process through which trypsin is enabled to enact its bactericidal and antitoxic functions. The intracellular functions of leucocytes, as we have interpreted them in this work, are dependent upon the same initial feature. Referring to the action of pancreatic juice, Foster states[76]: "The activity of the juice in thus converting proteids into peptone is *favored* by increase of temperature up to 40° C. [104° F.] or thereabouts, and *hindered* by low temperature."[77] That this likewise applies to the trypsin of the pancreatic juice is clearly shown in the following lines from Metchnikoff's pen: "From all their ingenious experiments Ehrlich and Morgenroth conclude that the fixative [Ehrlich's intermediary body or amboceptor; our oxidizing substance] is endowed with two different affinities: one for the red corpuscles and another for the complement [the trypsin-laden alexin]. Of these two affinities, the stronger is that which combines it with the red corpuscle, for it occurs at a very low temperature. In order that the fixative be enabled to

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[76] Foster: *Loc. cit.*, p. 282.

[77] All italics are our own.

combine with the complement, a much higher temperature is necessary."

In the light of our conception of the functions of the red corpuscles—*i.e.*, that it is merely a carrier of hæmoglobin, from which the serum can replenish itself with oxidizing substance as fast as this is used—the relationship between cell and oxidizing substance, or intermediary substance, logically coincides with the observations of Ehrlich and Morgenroth. The substance simply adheres to its feeder regardless of the temperature. Not so with the trypsin-laden alexin, however, for here the temperature-ratios of its trypsin and of the oxidizing substance are, as we have seen, practically co-equal, and, as trypsin requires a certain temperature to insure adequate functional activity, its *co*-substance, the oxidizing substance, must itself be brought to this temperature: *i.e.*, the "much higher temperature" to which Ehrlich and Morgenroth refer. We have seen how this purpose is reached, viz.: mainly by the phosphorus (absorbed by the leucocytes from the alkaline phosphates of the plasma) in the fibrinogen,[78] the blood's own source of heat. The direct part played by the fibrinogen and oxidizing substance in the hæmolytic process has caused some investigators to term "hæmolytic complement" the bodies which are constantly present in the blood-stream and increase in quantity when toxics are administered: *i.e.*, these two substances. It now seems obvious that, although they do take part in the hæmolytic process, they are only heat-producing auxiliaries, the true hæmolytic substance being the trypsin.

But the process involves the necessity of a mechanical combination capable of insuring the presence in the blood-stream of just enough trypsin to correspond with the fibrinogen in the blood-stream. How could this object be better subserved than, as is the case, by combining in the same cell, the neutrophile leucocyte, the two active constituents? Again, what more precise mechanism could we obtain than a granule of fibrinogen stopping up, as it were, a canaliculus leading up to the central or perinuclear vacuole in which the trypsin is stored and sud-

[78] We must emphasize the fact that the term "fibrinogen," as we understand it, is not intended to represent the body recognized as such by physiological chemists, though considerable kinship between the two exists.—S.

denly allowing enough of the latter to escape? As the need asserts itself,—impressed by the surrounding fluids upon the sentient exposed protoplasm of the leucocyte, thence communicated to its centrosphere—one, two, or many granules are unloaded, each being followed by a jet of the trypsin-laden fluid, but a jet only commensurate with the potential of the granule.

And experimental evidence is not lacking to show that such a process must prevail when toxics stimulate the adrenal system: "Under the influence of the repeated doses of pilocarpine," writes George Wilkinson,[79] in a study of the action of drugs on the leucocytes of the blood, "the granules become gradually less distinct, and eventually the protoplasm appears perfectly homogeneous and takes up the stain very feebly. In one of the animals this change was found to be very pronounced in so short a time as fifteen minutes after the first dose of the drug." All the work done in connection with cytolysis, especially that bearing upon red corpuscles, emphasizes not only the need of the mechanism we have outlined, but its presence. Indeed, *all* cells would be submitted to the destructive process to which these cells succumb when "fresh serum" is added even *in vitro* to the blood of "prepared" animals were it absent. In the light of our own views, we have here merely an exaggerated phenomenon, but a true picture of what would occur were fibrinogen, trypsin, and the oxidizing substance promiscuously mixed, as they are in *extra corpore* experiments. Here many red corpuscles, gorged perhaps with oxyhæmoglobin and enmeshed in fibrin filaments replete with phosphorus, suddenly find themselves imbedded, when fresh serum is added, in what is to them a seething mass. The leucocytes contributing their trypsin in the manner defined by Metchnikoff, and the aggressiveness of this corroding body being suddenly multiplied thirtyfold, as observed by de Dugern, the red cell soon succumbs, adding its own oxyhæmoglobin to the destructive medium surrounding it as soon as its stroma has been sufficiently disintegrated.

Such a fate for all vulnerable elements we deemed inevitable when, in the foregoing chapter, we discussed Buchner's

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[79] George Wilkinson: British Medical Journal, Sept. 26, 1896.

views as to the action of alexins. It is now plain that general destruction of cellular elements would prevail were the physiological co-ordination of all functions, including those of the blood, not as perfect as it is. Buchner's interpretation of the destructive action of alexins and of bacterial products is nevertheless justified; but it lacks the all-important controlling factors we have described to restrain this action within proper limits. Indeed, our organism produces trypsin to destroy bacteria which also produce kindred toxins capable of destroying us. It is primarily upon the integrity of our adrenal system and of the protective agencies that it governs, therefore, that our safety depends when bacteria, their toxins, vegetable poisons, and venoms penetrate the blood-stream, notwithstanding the barriers with which the intestinal and respiratory tracts are supplied to oppose their entrance therein.

But do the trypsin and the oxidizing substance simultaneously accumulate in the blood-stream? Trypsin being, as previously stated, the agglutinating body and the fixative the oxidizing substance, the following additional quotation from Metchnikoff's work[80] will show that such is the case: "The presence of the fixative, this other important element in immunity, could only be demonstrated in normal humors in exceptional cases and in small quantities. The agglutinating properties of these humors also showed themselves as but slightly developed, and devoid of importance in natural immunity. In *acquired immunity* against microbes we see, on the contrary, the bactericidal and agglutinative powers of the humors *increased to a great proportion.*"[81] As viewed from our standpoint, however, the bactericidal and agglutinative properties are both inherent in the trypsin; the oxidizing substance plays as elsewhere in the organism its rôle as a reagent, with the fibrinogen as the primary source of energy. This energy, manifested as heat, endows the trypsin not only with the power to convert toxins and diastases secreted by bacteria, toxalbumins, including vegetable poisons and venoms, into harmless products, as stated in the previous chapter, but it also enables it to destroy bacteria.

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[80] Metchnikoff: *Loc. cit.*, p. 264.

[81] All italics are our own.

All the foregoing facts seem to us to warrant the following conclusions as the manner in which bacteria, their toxins, and all other *albuminoid* poisons, whether the latter be traceable to imperfect physiological processes or to the introduction of these poisons from without, are converted in the organism into benign products:—

1. When the adrenal system, stimulated to unusual activity by a poison, increases the production of oxidizing substance, all the functions of the organism are correspondingly activated, including (1) those of the leucocytogenic structures, thus causing leucocytosis, and (2) those of the spleno-pancreatic system, thus giving rise to an excessive production of trypsin.

2. The general blood-stream thus becomes supplied with (1) an excess of oxidizing substance and (2) a larger proportion of neutrophile leucocytes which, on their way to the hepatic cells, absorb (3) a portion of the trypsin carried to the portal vein by the splenic vein.

3. The trypsin absorbed by the neutrophile leucocytes is mainly stored in their perinuclear digestive vacuole, into which most of the bacteria and other materials ingested by these phagocytic cells are digested.

4. An excess of heat-energy being necessary to insure the prompt and adequate digestion of these substances by the trypsin, this is provided for by a reaction in the canaliculi of the nucleus, between the oxidizing substance absorbed by the cell with the plasma and the phosphorus of the nuclein.

5. The trypsin which serves to destroy bacteria, toxins, etc., in the blood-stream, is derived from the neutrophile leucocytes and is secreted simultaneously with their fibrinogen granules, when their naked peripheral protoplasm is chemotactically stimulated by the toxic bodies in the plasma.

6. An excess of heat-energy being also necessary in the blood-stream to insure prompt and adequate disintegration, by the trypsin, of the bacteria, toxins, etc., present therein, this is provided for by a reaction between phosphorus-laden granules of fibrinogen discharged by the neutrophile leucocytes and the oxidizing substance of the surrounding plasma.

7. Both phagocytosis, carried on by wandering, endothelial, and other fixed cells, and the foregoing protective process carried

on in the blood-stream, thus owe their ability to convert bacteria and their toxins into harmless products to trypsin.

THE PHYSIOLOGICAL ACTION OF ANTITOXIC SERUM.

At the end of the previous chapter we stated that, judging from the stage of our analysis then reached, antitoxin contained blood-serum, alexins, trypsin, and oxidizing substance. In the light of the data submitted in the foregoing pages, each of the constituents of antitoxin seems to us to have acquired its due position as a physio-chemical agency.

The oxidizing substance, irrespective of its functions in the blood-stream when it combines with the fibrinogen, subserves all the other functions of the organism. Hence, the plasma must contain—and we have seen that it does—a constant supply of oxidizing substance over and above that utilized in the blood itself. The fibrinogen granules being supplied by leucocytes, they are doubtless distributed in measured quantities, as it were—just enough to sustain the blood's normal temperature or raise this if albuminoid poisons are present in the blood-stream. The increase of oxidizing substance insured by the adrenal overactivity which the poison itself causes compensates for extra oxygen used under these circumstances. Still, leucocytogenesis being commensurate with the surplus of adrenal activity, it becomes evident that at least the greater part of the oxidizing substance supplied to the blood-stream combines with the excess of fibrinogen formed to liberate heat-energy. It follows, therefore, that, while some oxidizing substance may be present in antitoxin, it cannot be considered as a prominent constituent of the substance. This does not prevent its disruptive influence upon toxics that are converted by oxidation into harmless products. Indeed, we have seen that phagocytic leucocytes absorb plasma, and with it oxidizing substance. As it is these cells which carry drugs, poisons, etc., introduced in the digestive canal, into the body itself, it is within their digestive vacuole that the poison first meets its foe. If a bacillus or an albuminoid: a toxin, a vegetable poison, etc., it is attacked by the trypsin; if an oxidizable body, by the oxidizing substance.

Buchner's alexin has likewise suffered from the analysis

submitted in the foregoing pages. Trypsin, we have seen, is the bactericidal agent of this body, the complement, the cytase, etc. To give alexin an autonomous position in our analysis does not, therefore, seem necessary.

THE ACTIVE PRINCIPLE OF ANTITOXIN. — The oxidizing substance and the alexins are thus eliminated from the list of agencies upon which the title of "active principle" might be bestowed. Trypsin, on the other hand, remains, having shown itself, indeed, as an autonomous body, distributed throughout the entire organism, endowed with all the attributes that an agency destined to chemically dissociate bacilli, their toxins, and other albuminoid poisons should possess. Though its full efficiency in the organism requires the heat-energy developed by the reaction between fibrinogen and the oxidizing substance, all the evidence points to trypsin as the active principle of antitoxin.

Though this coincides with Bordet's view that there is but one complement as against Ehrlich's that there is a multiplicity of them, our conception of the physio-chemical nature of this body is evidently sustained by the latter scientist's chemical analyses of this body, for "he believes," writes D. H. Bergey,[82] "the complement to be of the nature of an enzyme, and, therefore, the substance by means of which the immune body really brings about the solution of the corpuscles." That trypsin is an enzyme and that it dissolves the corpuscles in hæmolysis we have seen.

The rôle of trypsin and its relationship with the functions of the adrenal system as influenced by toxics is well shown by the experimental work of A. C. Abbott. Bergey, in the article previously quoted, also says: "It has been known for a long time that under the influence of fasting, excessive exercise, loss of sleep, etc., the organism is less resistant to disease than when functioning normally. It has been pointed out by Abbott[83] that, through the influence of alcohol, rabbits could be made more susceptible to infection by means of staphylococci and streptococci." In experiments by both of the above-named

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[82] D. H. Bergey: American Medicine, Oct. 11, 1902.
[83] Abbott: Journal of Experimental Medicine, vol. 1896.

observers[84] the following conclusions, among others, were reached: "The daily administration of alcohol *per os* to rabbits brings about a reduction in their circulating blood of hæmolytic complement [our trypsin]. . . . The administration of alcohol to rabbits induces not only a marked reduction in the complement content of their blood, but may cause, at the same time, a reduction in the specific hæmolytic receptor [our oxidizing substance] in the blood of rabbits artificially immunized against an alien blood. . . . The diminished complement content of the blood-alcoholized rabbits renders the animal more susceptible to the toxic action by an alien blood." It is plain, therefore, that insufficiency of the adrenals induced by a poison reduces the bactericidal and antitoxic agency, the complement: *i.e.*, the trypsin.

As previously stated, Metchnikoff credits the antitoxic properties to Bordet's fixatives (the oxidizing substance). The properties he ascribes to the latter bodies in the following lines are, therefore, those of the trypsin: "The fixatives offer many points of analogy with the antitoxins," says this author; "they are just as resistant to heating; they likewise show rather marked specificity; and, as is the case with fixatives, they are dispersed throughout the plasma." The same modifications of his interpretation of the nature of these substances is also applicable, however, when he writes: "Notwithstanding so many data in favor of the phagocytic origin of antitoxins, it is impossible to base this supposition upon rigorous and easily interpreted facts such as those possessed by science in favor of the phagocytic origin of fixatives." While the latter word, to meet our conception, should read "trypsin," Metchnikoff, we have seen, found that the diastase in the digestive vacuoles of his phagocytes was a trypsin, and that it was this body, therefore, which destroyed bacteria. Our analysis having shown that this process also applied to toxins and all other albuminoid poisons, and that, when one of these pathogenic agencies entered the organism, the trypsin was increased in the blood-plasma through the operation of three dominant factors: (1) primary overactivity of the adrenal system, (2) secondary over-

[84] D. H. Bergey and A. C. Abbott: University of Pennsylvania Medical Bulletin, Aug.-Sept., 1902.

activity of the spleno-pancreatic system, and (3) secondary over activity of the leucocytogenic structures, and that the trypsin supplied to the blood-plasma originated from leucocytes, it seems to us that we can legitimately conclude that:—

Bacilli, their toxins, and all other albuminoid poisons are converted into benign products by the same agency, trypsin, both in the leucocytes and in the blood-plasma.

This conclusion, however, awakens a question as to the manner in which antitoxic serum obtained from animals by means of repeated and gradually increased doses of injected toxins accumulates in the blood-stream. It would normally seem that the adrenal system, stimulated by the poisons, should, by loading the circulation with oxidizing substance, cause the liberation of considerable heat-energy, and give rise to an increase of the trypsin's activity sufficient to involve the destruction of all cellular elements. But we must not lose sight of the fact that, while leucocytosis and a marked increase of trypsin-production are caused by an excess of oxidizing substance in the plasma, the leucocytes obtain from the intestinal canal the necessary proteids to create not only fibrinogen, but also the myosinogen, lecithin, hæmoglobin, etc., required by the organism's general routine work—since we refer to presumably healthy animals. The formation of fibrinogen is, therefore, commensurate with the proportion of proteids ingested; and the primary source of heat-energy, that with which the oxidizing substance combines, is thus only just sufficient to preserve the blood's normal temperature.

A proof of this is afforded by Widal's reaction. We have shown that agglutination was a property of trypsin. Typhoid fever we shall see in the next volume is essentially a disease in which the absorption of proteids is inhibited mainly through impaired leucocytogenesis, owing to disease of the intestinal lymph-follicles: a fact itself demonstrated by the identity of the disease as the *only* one among the greater febrile processes in which, in cases following their regular course, the proportion of leucocytes in the blood is decreased. As a result, the quantity of fibrinogen in the blood-stream is limited in proportion as the number of lymph-follicles involved is great. Nevertheless the oxidizing substance, *an internal secretion*, the trypsin,

an internal secretion, are continuously produced in excess, the former only burning up what fibrinogen is formed by the small contingent of available leucocytes, and the protective destruction of bacteria, toxins, catabolic products, etc., being correspondingly reduced. But heat-energy is a measurable quantity, and that produced through the combination of fibrinogen and the oxidizing substance can only enhance the activity of a proportionally limited amount of trypsin, thus leaving a surplus which accumulates in the blood-stream. The blood of a typhoid-fever case thus contains a proportion of trypsin which no other disease (owing to the absence of lesions of the lymphatic follicles and particularly of the agminated follicles or Peyer's patches) shows, and in Widal's test trypsin acts upon the bacilli when added to a culture precisely as trypsin does upon any albuminoid body *extra corpore*. The movements of the germs cease as soon as their surface is being softened by the trypsin; this softening causes this surface to become adhesive, and they therefore adhere to one another: *i.e.*, become agglutinated, forming "clumps."

While further indicating the great value of Widal's reaction as a diagnostic feature, it seems evident to us that, if the general frame-work of our conception of all the physiological and pathological phenomena involved did not rest upon a solid foundation, it could hardly be accounted for without indulging in hypothetical conjectures. Again, if the entire field of the physio-chemistry of the blood is scrutinized,—as we have done,—it will be found that the only agency that it could contain to which this action upon bacteria and other albuminoid bodies could be ascribed is trypsin. It seems to us, therefore, that we can confidently conclude that:—

Trypsin is the dominant active principle of antitoxin.

The Uniformity of All Antitoxic Sera.—This deduction involves another which tends greatly to simplify the entire problem of serum-therapy, both as to the production of serum and its use in disease. We have fully shown, we believe, the relationship between the adrenal system and poisons. That a poison capable of stimulating the anterior pituitary body always gives rise to the excessive production of the oxidizing substance, trypsin, and leucocytes,—when the organs represented are nor-

mal,—need hardly be repeated. Again, we have seen that the quantity of oxidizing substance produced by the adrenal system is commensurate with the stimulating activity the poison injected can excite in that system. As the quantity of oxidizing substance produced correspondingly enhances the functional activities of the spleno-pancreatic system and of the leucocytogenic structures (all else being normal), it is evident that the toxic that will most actively stimulate the adrenal system without causing adrenal insufficiency will produce the greatest quantity of trypsin. This body in turn being dissolved in a given quantity of blood-serum, the efficiency of antitoxic serum obtained as to units will correspond with the stimulating power of the toxic employed. In other words:—

The injection of different toxins into healthy animals, as now practiced to obtain immunizing sera of various kinds, including antitoxin, always leads to the same result: i.e., to the production of a serum containing trypsin as its dominant active principle.

The proportion of trypsin in a serum thus obtained is commensurate with the stimulation of the adrenal system that the toxic injected can cause without giving rise to adrenal insufficiency.

Again, the use of toxins to obtain antitoxic serum—a feature which limits the therapeutical use of the latter by inspiring fear of complications—is not necessary in the light of our views. Indeed, Ehrlich has immunized animals by means of injections of ricin and abrin to the effects of fatal doses of these poisons: a proof that these agents greatly increased the production of trypsin in the experimental animals. Since all poisons capable of safely stimulating the adrenal system produce a serum containing trypsin, we may therefore conclude that:—

Bacterial toxins may be replaced by equally active toxalbumins or vegetable alkaloids to obtain antitoxic serum from animals.

This raises a question as to whether a more efficacious agent than antitoxin could not be obtained by toxics capable of raising the adrenal functions to a higher potential, thus increasing the proportion of trypsin in a given quantity of serum. The answer seems to us, at least, to be embodied in the following editorial comment[85]:—

[85] Journal of the American Medical Association, Nov. 1, 1902.

"It will be remembered that when the soluble bacterial toxins of the bacillus of diphtheria and of the bacillus of tetanus were discovered the hopes ran high that in this way would be explained the action of all pathogenic bacteria; but soon these hopes met with disappointment. With this disappointment also fell to the ground the hope that specific antitoxic serums could be produced for all or most of the bacterial diseases, just as in the case of diphtheria or tetanus. The conditions did not prove to be so simple as first thought. . . ." Indeed, the specificity that a serum was supposed to possess, when obtained with a specific toxin, seems to us to have proven misleading. But it is not upon a high potential that our hopes for better results must rest, but upon a more scientific adjustment of the serum to morbid conditions.

THE LIMITS OF SERUM-THERAPY.

What we mean by scientific adjustment of a serum to morbid conditions is the judicious use of the dominant triad upon which the organism depends to counteract the morbid effects of bacteria, their toxins, and other poisons: *i.e.*, (1) trypsin, (2) fibrinogen, and (3) the oxidizing substance. This will be illustrated by briefly reviewing their rôle in the more important of the general infections.

Typhoid Fever and the Typhoid State.—In an excellent review of the present status of serum-therapy F. A. Packard and R. N. Willson[86] introduce the following remarks: "A great hindrance to the development of serum-treatment up to the present time has been the failure to consider the constant lack in infections of sufficient quantities of both the binding body [our oxidizing substance] and the complement [our trypsin], though Wassermann has, as stated, shown in a series of experiments, that they can be supplied, and that, by means of their addition, results can be obtained that have heretofore seemed impossible. He has found that, by injecting *normal serum* (thus supplying the end-body and complement) together with immune serum, he can immunize against virulent cultures and toxins that produce early death when combated by the immune

[86] F. A. Packard and R. N. Willson: American Journal of the Medical Sciences, Dec., 1902.

sera alone, which contain little else than the immune body or the binding substance. . . . He found that normal serum from cattle (beef) could be used with typhoid immune serum—*e.g.*, that guinea-pigs injected with three loops of living culture (typhoid) and in a half-hour with 0.5 cubic centimeter of typhoid immune serum mixed with 4 cubic centimeters of fresh normal ox-serum, all survived in good health, while control animals injected with *normal* serum *or immune* serum alone all died in twenty-four hours."[87] This series of experiments seems to us to demonstrate the correctness of our views. Indeed, it is obvious that, *while the immune serum furnished trypsin, the normal serum furnished fibrinogen* (the oxidizing substance being too limited in quantity to add energy to the animal's living blood); this fibrinogen, by combining with the oxidizing substance in the injected animal's blood, liberated enough heat to raise the trypsin's energy to the required level, and it chemically dissociated not only the bacteria, but their toxins.

But herein lies the adjustment to which we have referred: Widal's test has enabled us to show that fibrinogen is precisely the missing agency in typhoid fever; the ox-serum, therefore, supplied this substance. But we have also seen that it is the *only* disease in which the fibrinogen is lacking to such a marked degree, and that Widal's test owes its value to this fact. What, then, about all other diseases?

If the morbid process in typhoid fever is now traced to its source, it will become evident that it is partly ascribable to *inhibited phagocytosis*, and not altogether to the fact that the number of cells that are able to take up proteids in the intestinal canal is more or less reduced. Fibrinogen is thus inadequately furnished to the blood-stream. Indeed, were the cells produced, as they are when leucocytosis occurs, even though they could not reach the intestinal foodstuffs, fibrinogen would be formed in the neutrophile cells. In the light of the analysis we have submitted, the heat which energizes the trypsin in the digestive vacuole of a phagocyte is mainly due to the reaction between the nuclein of its nucleus and the oxidizing substance absorbed by the cell with the plasma. The cell, therefore, does not require fibrinogen, but the bacteria it ingulfs are them-

[87] All italics are our own.

selves digested and converted into useful secretions, one of which is fibrinogen, its phosphorus being acquired from the alkaline phosphates of the plasma.

This exemplifies an exceedingly beautiful provision of Nature, if examined closely. Indeed, leucocytosis, when not inhibited as it is in typhoid fever, being commensurate with the degree of intoxication (the adrenal system acting as touchstone, as it were, for the morbid process) the fibrinogen derived from the bacteria ingested by the surplus of phagocytes is evidently intended to supply the needs of the febrile process, thus avoiding a derangement of the general mechanism of all functions. As it is only inhibited to a marked extent in typhoid fever, however, it becomes evident that in all other febrile processes and intoxications that are not sufficiently severe to overwhelm the adrenal system and cause immediate insufficiency (in which bacteria penetrate the blood-stream) the additional *fibrinogen* required for the febrile process is obtained at the expense of the bacilli ingested by the surplus of phagocytes, besides that acquired from proteids; the *trypsin* through overactivity of the spleno-pancreatic system; the *oxidizing substance* through overactivity of the adrenal system. In other words, the dominant triad of the protective process is always available in diseases in which pathogenic organisms penetrate into the blood. On the whole, it seems clear to us that:—

When leucocytogenesis is not inhibited:—

1. The plasma is provided with the three agencies, fibrinogen, trypsin, and oxidizing substance, that enable it to dissociate the bacteria that phagocytes do not ingest and digest.

2. The bacteria ingested by phagocytes are converted in these cells into peptones, myosinogen, and fibrinogen, the phosphorus being derived from the alkaline salts of the plasma.

3. The system is thus supplied with the surplus of fibrinogen required to sustain the febrile process, even though the proteids obtained from the intestinal canal by the cells be small.

When leucocytogenesis is inhibited to any marked extent, as it is in typhoid fever:—

1. The absorption of proteids from the intestinal canal and phagocytosis are correspondingly reduced and the formation of fibrinogen is inadequate.

2. The oxidizing substance and the trypsin is nevertheless formed in excess owing to the prophylactic functional activity of the adrenal system.

3. The trypsin being deprived of the heat-energy of which fibrinogen is the primary source, it remains unused and accumulates in the organism, as shown by the Widal reaction.

4. The excess of oxidizing substance produced proportionally enhances general cellular metabolism, and, the formation of peptones and myosinogen being reduced owing to inhibited leucocytogenesis, the "typhoid state" is engendered.

That these conclusions are based on sound premises is shown by the following quotations from two papers, one by Naegeli,[88] the other by M. L. Richardson.[89] The former investigator found that "the *neutrophile* cells decrease rapidly in the first stage of typhoid fever, soon reach the half of their usual number, and gradually further decrease up to the stage of defervescence. In the convalescence they begin to increase, at first slowly, and then rapidly. It is usually only after many weeks that the normal figures are regained."

The absence of fibrinogen, by depriving the trypsin of its bactericidal properties, must necessarily give free sway to the latter. Richardson writes as follows: "If we take the fresh blood-serum from a typhoid patient at any stage of the disease or convalescence and combine it, for example, with an equal quantity of a bouillon culture of the typhoid bacillus, we get, in the vast majority of cases, not destruction, but abundant multiplication of the typhoid organisms." Still, if all our estimates of the manner in which the results of the experiments *in vitro* previously analyzed are sound, normal serum should supply the heat necessary to energize the trypsin. Richardson also satisfies this feature of the problem by the following remark: "If we introduce the mixture of serum and bacilli into the peritoneal cavity of a normal guinea-pig, we find that there is not only a complete absence of multiplication of the bacilli, but there is absolute destruction and disappearance of the organisms": *i.e.*, Pfeiffer's phenomenon.

It now becomes apparent that it is not by adding an anti-

[88] Naegeli: Correspondenz-blatt für Schweizer Aerzte, No. 18, 1899.

[89] M. L. Richardson: The Journal of Medical Research, vol. vi, July, 1901.

toxic serum, the active principle of which is trypsin, to a blood-stream already overburdened with trypsin that we can hope to overcome typhoid fever and kindred disorders in which fibrinogen is inadequately formed. If, in addition, we realize that an active febrile process (the organism's main protective resource against bacilli and their toxins) indicates that the adrenal system is in full activity, and that the plasma contains an ample proportion of oxidizing substance besides trypsin, it seems but logical to conclude that:—

In febrile diseases attended with hypoleucocytosis and in which an excess of trypsin is found to exist (by the Widal or other tests) a serum rich in FIBRINOGEN *should be administered.*

Indeed, Richardson[90] found, in his observations in forty-one typhoid patients at different stages of the disease, that "in the stage of convalescence or falling temperature, the normal element returns apparently to the blood, and a corresponding destruction of bacilli takes place." He also remarks almost prophetically,—if our views are sound,—though he ascribes the hypothetical effects, in accord with Ehrlich and others, to the "immune substance" (our oxidizing substance): "We can, therefore, hazard a guess why serum-therapy in typhoid fever and allied diseases has made so little progress. We have been giving a serum loaded with immune element with which the patient was perhaps already surfeited, and we have neglected to give the element that was necessary to make active powerful agencies already present in the patient's blood. Apparently, therefore, we should give to most of our typhoids normal serum." We have seen, by Wassermann's experiments, that fresh ox-serum sufficed to save infected guinea-pigs.

Can we use fresh serum in human beings? The cytolytic action of the serum of one species when introduced into the blood-stream of animals of another species is well known. In the light of our analysis this is accounted for by the fact that the blood introduced too suddenly augments the proportion of trypsin in the host's blood (trypsin being practically limited, we have seen, to the leucocytes during health), and, finding the fibrinogen and oxidizing substance necessary to greatly increase its dissociating energy, it attacks the red corpuscles as it would

[90] Richardson: *Loc. cit.*, p. 199.

bacteria. That this is true is shown by the fact recorded by Bordet[91] that agglutination was the first effect of hæmolysis produced in this manner. The quantity of serum injected and the intervals between the injections thus become the ruling factors of the use of normal serum. This is sustained by the experiments of Cantacuzène[92] and others.

But we refer in this connection only to normal serum, as against that of immunized animals or animals in which even the blood of another species has been injected. Indeed, as is well known the latter acquires through the procedure a marked increase of hæmolytic power, simply through the fact, in our opinion, that the alien serum acts as a toxic upon the adrenal system and gives rise to an active production of the blood's protective bodies: a feature which can be clinically utilized to great advantage by avoiding large doses.

Richet and Héricourt (who also first suggested immunization by means of the blood-serum of immunized animals) found experimentally, as is well known, that the injections of dog-serum were completely non-toxic if collected with due care. Richet[93] used hypodermic injections of this serum in tuberculosis, pulmonary and laryngeal. Both the local and general phenomena were improved, the patients gaining several pounds in weight. The serum proved absolutely harmless physiologically. Roger[94] experimentally found that the treatment reduced the virulence of the bacillus. Semmola[95] obtained beneficial results in but two out of ten cases. This is readily accounted for in the light of our views, for the serum can only be valuable in the advanced stages: *i.e.*, when hypoleucocytosis by wasting, a febrile process, etc., are present owing to involvement of the leucocytogenic glands. Our aim, however, is to show that the blood of some lower animals can be safely used in human beings. Immunized horse-serum and goat-serum have also been employed without giving rise to untoward phenomena, and the use by Wassermann of ox-serum in guinea-pigs suggests that this readily-obtained serum can likewise be used with due pre-

[91] Bordet: Annales de l'Institut Pasteur, vol. 1896.
[92] Cantacuzène: Annales de l'Institut Pasteur, vol. 1900.
[93] Richet: La Semaine Médicale, Jan. 28, 1891.
[94] Roger: Bulletin de la Phthisie Pulmonaire, Paris, No. 3, 1891.
[95] Semmola: Internationale klinische Rundschau, Nos. 25, 26, 1891.

cautions. Brodie has found, however, that, of all sera obtained from domestic animals, horse-serum was the least toxic. On the whole, the literature of this therapeutic method and the foregoing line of reasoning seem to us to warrant the following conclusions:—

The normal serum of certain animals, particularly the horse, ox, cow, goat, and dog, contains enough fibrinogen to render its use in small and frequently repeated doses advantageous in febrile processes attended with hypoleucocytosis and an excess of trypsin. Horse-serum, being the least toxic, should be given the preference.

Diphtheria, the only disease which may be said to have found in antitoxin, thanks mainly to the splendid labors of Behring, a specific antagonist, presents, it seems to us, pathological characteristics of an opposite order. Here leucocytosis is a prominent feature of the morbid process,—as long as the adrenal system is functionally overactive,—and, since antitoxin does prove unquestionably effective when the whole subject is studied with due care, it follows, if our views are sound, that the neutrophiles are able to furnish the blood with enough fibrinogen to afford, in conjunction with the oxidizing substance, the heat-energy required by the trypsin which the injected antitoxin contains. Such being the case, the disease must follow a lethal course merely because of the lack of trypsin. How is this absence of trypsin engendered, or, if there *is* trypsin in the child's plasma, why does it fail to antagonize the pathogenic elements?

A feature emphasized by Metchnikoff, and that our analysis has sustained, is the absence of trypsin from the plasma. According to our own interpretation of experimentally demonstrated facts, such a condition of the blood only occurs when it is completely devoid of morbific products of digestion wastes which the leucocytes themselves cannot submit to complete cleavage. Briefly, it may be said that under normal conditions the blood does not contain trypsin. And this may be demonstrated by a very familiar bacteriological fact: *i.e.*, that, using Stengel's words, "the most characteristic cultures are obtained upon blood-serum."

A direct application of this fact, however, would mislead us. In other words, we cannot say that it is because the blood

contains no trypsin that the bacilli increase rapidly in a diphtheritic child's plasma; indeed, diphtheria presents the characteristic, in human beings and during life, of showing but few bacteria in the blood-stream. "It is a local infection, due to the presence and development of the bacilli in the pseudo-membrane," writes McFarland, "but is accompanied by a general toxæmia resulting from the absorption of a violently toxic substance produced by the bacilli. The bacilli are found only in the membranous exudation, and most plentifully in its older portions." And were it otherwise, the presence of bacteria in the blood-stream would not account for the absence of trypsin. There is, therefore, another cause for this phenomenon.

We have submitted the reasons that have led us to conclude that the leucocytes, when on their way to the liver, absorb the greater part of the trypsin poured into the portal system by the splenic vein. The excessive hepatic functional activity which accompanies a corresponding activity of the adrenal system, renders the probability that any trypsin finds its way into the general circulation very remote. It is, therefore, imprisoned in the leucocytes. But another blood-cell has experimentally shown considerable affinity for trypsin: *i.e.*, the red corpuscle. Indeed, Ehrlich and Morgenroth and Bordet have demonstrated that the alexins are absorbed by these cells, and we have seen that Metchnikoff found the active body of the alexins to be trypsin. Another feature of the whole process upon which Bordet lays stress is embodied in the following words: "It is proper, therefore, to ascribe to the stroma the property that red cells show of absorbing alexin in the presence of sensitizing substance" (our oxidizing substance).[96] It thus becomes evident, seeing that the blood-stream always contains oxidizing substance, that whatever vestige of trypsin may happen to pass beyond the portals of the liver is at once taken up by the red corpuscles. That under such circumstances the child's plasma should be completely deprived of trypsin is evident.

Still, why do the leucocytes, gorged with trypsin as they are, not convert the toxins in the blood-stream into benign cleav-

[96] Renault: Archives Générales de Médecine, Dec., 1900.

age products? Being greatly augmented in number through adrenal overactivity, it would seem as if they should be capable of doing so. Such is the case in mild infections or when the child's thymus and partly developed adrenal system can sufficiently prolong the fray. But when they cannot, another cause appears, one that illustrates vividly the scientific value of Metchnikoff's labors: *i.e.*, the phagocytes are unable to *reach* and *destroy* the *source* of the toxins. Indeed, the bacilli are in the false membrane. Multitudes of cells crowd to the respiratory passages or other surfaces to destroy the local focus of infection. And the pseudomembrane is itself but an extensive cemetery of protective cells in which the cadavers are more numerous than the particles of soil! But what is this exposed surface when compared with the vast immunizing field which the capillary system represents and into which the contraction of the central vascular trunks incident upon adrenal overactivity forces, not only the poison, but the laboratory in which it is formed?

We can now understand, it seems to us, why the virulent toxins of the diphtheria bacillus accumulate so rapidly in the blood-stream and soon cause what any other virulent poison does: *i.e.*, arrest of adrenal functions, after the preliminary signs which denote the stage of insufficiency. . . . "The pallor is extreme; the face has an ashen-gray hue," writes Osler; "the pulse is rapid and feeble, and the temperature sinks below normal." We can understand also how antitoxin acts and why *delay* in its use compromises the issue; indeed, why it *insures* death in a severe case. The trypsin of the antitoxin finds in the plasma the fibrinogen and oxidizing substance it requires to develop its full energy, and it soon converts the toxins into harmless agencies. But this *only* occurs when organic lesions have not been given time to hamper the mechanism of the vital processes; that is to say, when necrotic foci in the liver, heart, *pancreas, spleen,* etc., have not been given time to form, and while the adrenal system is still able to recover its functions.

And we have evidence of the adrenal system's work in some cases; for what are the eruptions and other untoward phenomena that occasionally follow the use of antitoxin but evidences that the blood is loaded with waste-products that the

normal channels cannot eliminate with sufficient speed? Indeed, these eruptions show that the scales have been turned; that antitoxin—devoid itself of all toxic attributes when pure—has conquered its foe, and that the immunizing field, the peripheral capillary system, is ridding itself of the remains of the fray. That the following conclusions are warranted seems to us evident:—

While the blood-stream in diphtheria is adequately supplied with oxidizing substance and fibrinogen, it is deficient in trypsin; hence, toxins rapidly accumulate.

The active principle of antitoxin being trypsin, it becomes active in the blood-stream owing to the presence therein of the fibrinogen and oxidizing substance, and converts the toxins into benign cleavage products.

Antitoxin is curative if used sufficiently early in diphtheria, and harmless if used in any disease with which diphtheria may be confounded.

Tetanus.—This is another disease in which bacilli have been found only at the seat of inoculation, but not in the blood. The toxins are developed so rapidly, however, that, as shown by Kitasato, only animals from which the inoculated area had been excised one-half hour after inoculation remained well. All the conditions reviewed under the last heading, namely: (1) the absorption of trypsin by leucocytes and erythrocytes, (2) the impossibility on the part of the phagocytes to protect the system by destroying the source of the toxins, prevail, therefore, and it is the only disease which has afforded any evidence of *remote* kinship with diphtheria as regards the effects of antitoxin when used *early*.

But here another course of events is inaugurated. We are not dealing with a poison which tends first to stimulate the adrenal system and then, by exhausting the anterior pituitary body, to bring on insufficiency soon followed by arrest of adrenal functions, but with a virulent toxin which does not, to any extent, primarily stimulate this system. Insidiously, and almost from the start, it gives rise to adrenal insufficiency, and steadily the products of metabolism accumulate in the blood. We have throughout this work given reasons that seem to us to demonstrate that the toxin is not the direct cause of the

tetanic convulsions, but that these should be ascribed to the accumulation of products of metabolism incident upon inhibited oxidation. Tetanus neonatorum, epilepsy, hydrophobia, eclampsia, etc., are kindred conditions, as we shall see in another volume. Care must be taken, however, not to confound the convulsions induced by these various forms of sepsis with those observed in strychnine poisoning. This form of "tetanic" convulsions is due, we have seen, to hyperoxidation.

Tetanus antitoxin would undoubtedly show far better results than can now be credited to it judging from the literature of the subject, could it be used, not when the convulsions have begun—the second stage—as is now generally the case, but very soon after the receipt of the injury: *i.e.*, before the adrenal functions are seriously compromised. But how distinguish the exposed cases when we know that even slight injuries may initiate the morbid process when received in stable-yards, gardens, roads, etc., the bacillus being a common saprophyte found in manure, dust, soil, etc.? Better means may perhaps suggest themselves in the next subdivision of immunity to be considered.

What shall we say of the multiplicity of other sera that have been introduced from time to time: the antistreptococcic, antipneumococcic, antituberculous, antivenomous, and the more recently introduced sera calculated to combat the plague, dysentery, yellow fever, scarlatina, anthrax, leprosy, glanders, pertussis, syphilis, malaria, and other disorders? Herein lies, it seems to us, the misleading factor which has suggested that specificity could be considered as an element of these various sera. Indeed, all these agents are beneficial because they all stimulate the adrenal system—as does any active agency introduced into the blood-stream. But they are not specific, if our views are sound; they only differ essentially in the proportion of trypsin they contain: the unused product of the artificially stimulated adrenal system of the purveying animal.

Briefly the following conclusions seem to be warranted by the foregoing data:—

1. Precisely as is the case with drugs, so do the different toxins stimulate the anterior pituitary body with more or less vigor, or depress its functions.

2. Precisely as is the case with drugs, so are the different toxins endowed with specific attributes, each toxin reacting primarily upon the anterior pituitary body in its characteristic way.

3. The various sera introduced, including anthrasin, are all similar in the sense that they contain the same constituents, the dominant active principle in all being trypsin.

Still, the use of the many sera introduced has shown that they differ from one another symptomatically, and in a way which trypsin, alone, in the light of our statements, could not explain. Even a cursory review of these effects will show, however, that we are dealing with symptoms that denote a mere increase in dosage of certain secondary constituents—a feature which accounts for our use of the word "dominant" in respect to trypsin as an active principle. Which are these secondary constituents? We have emphasised the fact that an increased production of trypsin was caused when a toxin or any other poison in the blood-stream enhanced the functional activity of the adrenal system, because that of the spleen and pancreas was also enhanced, though secondarily. That the functions of the *thyroid* gland, under these circumstances are likewise raised to inordinate activity is self-evident. The use of a specific toxin, therefore, must indirectly cause this organ to supply the blood with a proportion of thyro-iodine commensurate with its ability to stimulate the adrenal system. It seems clear to us, therefore, that:—

4. The various antitoxic sera are more or less active in proportion as the quantity of thyro-iodine contained in them is great.

5. The proportion of thyro-iodine in a given serum is commensurate with the degree of stimulation to which the adrenal system of the supply-animal is subjected by the toxin employed to obtain this serum.

But this introduces another factor: *i.e.*, the part played in the effects of the serum by the agencies added to it to insure its preservation, *i.e.*, carbolic acid (Behring), camphor (Roux), trikresol (Aronson), etc. They are all adrenal stimulants, fortunately, and can only, therefore, enhance its effectiveness. Still, they are all capable of giving rise to phenomena that may suggest specific qualities quite foreign to the serum itself, and which drugs, judiciously handled, can replace with advan-

tage. It seems to us, therefore, that we can legitimately conclude that:—

6. The use of antitoxic serum or of the various sera introduced is only indicated in morbid processes characterized by a deficiency of trypsin.

In all other pathological conditions drugs are productive of better effects, because these can be scientifically controlled.

ARTIFICIALLY PRODUCED IMMUNITY.

The foregoing deduction seems to us to embody a far-reaching meaning in connection with the subject which is now to claim our attention. If the entire domain of immunity is scrutinized, it will become apparent that the effects of all inoculations are similar: they all react more or less promptly and more or less vigorously upon the adrenal system; and upon the *character* of this stimulation depends the duration of degree of the protection conferred upon the inoculated subject. Here we no longer have as active factors benign sera of varying strengths which require two complementary bodies in joint action to manifest their beneficial activity; we are dealing with toxalbumins, far more active than many of the more potent alkaloids of our pharmacopœia, but which present the same physiological attributes as alkaloids and all drugs and toxins.

Still, a distinction asserts itself in this connection, which will serve to give each of the forms of immunity artificially produced its true physiological bearing. Indeed, we must not lose sight of the fact that there is a difference of vast practical importance between the action of a dose of toxins introduced artificially into the blood-stream and the manner in which a disease is developed in the organism either through the entrance of pathogenic germs directly into the blood or, as in diphtheria and tetanus, through the intermediary of a peripheral focus of these germs. Whether these myriads of toxin laboratories be in the blood or outside of it matters little as long as their products enter the blood. *Disease* means the introduction of these *sources* of toxins, which rapidly increase in number in blood devoid of trypsin, while artificial *immuniza-*

tion means the introduction not of the bacteria, but of their products: the toxins themselves. These do not reproduce any more than the alkaloids of plants reproduce; they react with more or less vigor upon the adrenal system, precisely as do these alkaloids or other drugs. Indeed, if, instead of "toxins," they were called, as are alkaloids, "medicines," their use would inspire no more fear of complications than do the former, and their true position in therapeutics would be accorded them.

Hydrophobia. — The distinction may perhaps be more clearly shown by briefly submitting our interpretation of the manner in which this dread disease is developed in the organism, and the difference between this process and that following vaccination against rabies, as practiced at the Pasteur Institute of Paris.

Have we in the wound, as in the case of tetanus, a focus from which toxins are gradually developed? Bacteriologists have not as yet determined the nature of the exciting agent of rabies, but the development of the disease recalls that of tetanus. As is the case with the toxins of the tetanus bacillus, the potential of the toxic body of rabies is such that the stage of adrenal stimulation passes practically unperceived, and the adrenal system gradually lapses into insufficiency. The amount of trypsin, oxidizing substance, and fibrinogen in the blood and cells is reduced in proportion, though life's processes continue, and waste-products are continuously being elaborated. The day finally comes, however, when the accumulation of *physiological* poisons is such that the usual symptoms, including convulsive paroxysms, *i.e.*, the rabies, appear. But why does the blood of a rabid animal never contain the virus?

We are incidentally afforded another proof of the correctness of our views in two of the leading newer conceptions we have submitted: *i.e.*, the principle that toxic elements are destroyed in the peripheral capillaries by contraction of the muscular vessels from which they receive their supply; and the identity of the minute elements of the central nervous system as blood-channels. That the cerebro-spinal system is the seat of accumulation of the virus of hydrophobia, and that Pasteur, whose genius will serve as beacon for all generations, employed the desiccated medulla of rabbits in his vaccination against

rabies, need hardly be recalled,—any more than the fact that by using medullæ in various stages of desiccation he was able, with Roux and Chamberland, to completely immunize dogs from the bites of rabid animals.

When the method is employed in human beings, a small piece of desiccated cord is rubbed up in sterile bouillon and some of the fluid thus prepared is injected at intervals. Wherein does this method differ, in the light of our views, from injections of an equally active alkaloid? Simply in this: We have seen that poisons differ as regards the energy with which they stimulate the adrenal system; by using the toxin of a given bacillus we are at least reasonably certain that the vigor with which the adrenal system will be stimulated will prove adequate to cause the production of sufficient oxidizing substance, fibrinogen, and trypsin to fully master the morbid process: a result which a weaker agency might fail to insure. There is a degree of precision in the use of the *méthode intensive,* therefore, that the use of other agents to offset the disease would not afford.

Still, we have only, so far, referred to the manner in which the morbid effects of germs and toxins are counteracted; another question presents itself, however: *i.e.,* How is the immunity prolonged, as it is by vaccination against small-pox, for example, and various diseases? This may be illustrated by a brief reference to vaccination.

Vaccination against Small-pox.—In this method, as now practiced, the "lymph" obtained from pocks of young calves is the inoculating agent. The nature of the infecting agent as in the case of rabies has remained undiscovered; but it evidently differs as to its mode of action from that of the virus of the latter disease, since, instead of insufficiency, it gives rise to a febrile reaction and other phenomena of marked adrenal overactivity. That this adrenal reaction sometimes exceeds its normal limits is illustrated by the cases of tetanus that have been recently observed after vaccination. Under these circumstances adrenal insufficiency occurs precisely as in true tetanus, but is preceded by a primary stage of overactivity which the adrenals of the various subjects are not able to stand.

We have clear evidence here that inordinate functional

activity of the adrenal system has been excited; but this means that all organs concerned in the immunizing process, besides the adrenals, the spleen, pancreas, etc., and the various structures concerned in leucocytogenesis, have been roused. Indeed, the period between the moment of inoculation and the entire disappearance of the virus from the blood-stream represents a continuous stage of greatly exaggerated function—akin to that to which the subject would have been submitted had he gone through the disease. The adrenal system and all the other organs the functions of which it energizes, have, during all this time, been the seat of unusually active nutrition, and the return to their previous condition is by no means sudden. Indeed, it occupies years sometimes—the years during which the subject is immune to the exciting agent of small-pox. Notwithstanding the severity of the reaction, however, vaccination is likewise benign because it does not introduce into the blood the source of the poison, the micro-organism, but a minute dose of the poison itself, which cannot therefore increase in quantity or power.

The foregoing conception of the manner in which preventive "inoculations"—an unfortunate term, by the way—produce their beneficial effects, seems to us applicable to all measures of this kind, whatever be the disease from which protection is sought. The recent favorable evidence recorded by British army surgeons as to the use of typhoid bacillus sterilized cultures in Africa is noteworthy, for we have seen that fatigue and other untoward features to which a soldier is exposed during campaigns tend greatly to weaken the functional energy of the adrenal system and, therefore, his vulnerability to disease. Haffkine's preventive inoculations against plague have likewise demonstrated their value, etc. Briefly, all forms of vaccination endow the inoculated subject with enhanced activity of the adrenal system and, therefore, of all structures which take part in the defense of the body.

Natural immunity, *i.e.*, the innate power to resist disease, is ascribable, it seems to us, to identically the same cause. Of course, the susceptibility of some individuals to certain diseases while they are immune to others is not to be overlooked; but this introduces features of another kind that will receive attention

in another volume. These features, however, do not modify the position of the adrenal system in all processes connected with immunity and, we may add, with the pathogenesis of all general intoxications. Indeed, all the testimony and lines of reasoning we have adduced seem to us to warrant the conclusion that:—

The power of the organism to antagonize the constitutional effects of pathogenic germs, their toxins, and other poisons, is directly proportionate, all else being equal, to the functional efficiency of the adrenal system.

IMMUNIZING MEDICATION.

The foregoing conclusion obviously suggests that since certain remedies greatly increase, even when administered by the mouth, the functional activity of the adrenal system, we might, by the *judicious* use of such remedies, protect the organism against pathogenic germs, their toxins, and all poisons that the protective apparatus can overcome when its efficiency is raised to its highest potential. In other words, it suggests that, prior to exposure to infectious diseases or during epidemics, after injuries received in places thought to contain tetanus saprophytes, after bites from presumably rabid animals or from venomous animals, etc., we might be able to cause, in our blood-stream, a sufficient accumulation of phagocytes, trypsin, fibrinogen, and oxidizing substance to offset the life-destroying tendency which all these bodies exhibit. The contents of this entire work seems to us to sustain such a deduction.

If we recall the energy with which certain agents: quinine, for instance, force blood into the peripheral capillaries, by causing contraction of the central vascular trunks and other vessels supplied with muscular walls, it will become apparent that the presence of this remedy in the blood not only excites the adrenal system to unusual activity, but that the vast immunizing field of the organism is being utilized to destroy the alkaloid. The headache and the superficial heat, the suffused face, the hard pulse, etc., testify to this. But we are dealing with an inoffensive agency,—if properly used,—and its value as a prophylactic has been emphasized by those writers who

speak from the standpoint of experience, including Laveran and Maurel. Now that the source of the parasite has been traced to the mosquito, we can readily understand the nature of the prophylactic process, *i.e.*, dissociation of the morbific agent in the peripheral capillaries into which the system's protective agencies have accumulated. But quinine is not the only agent capable of producing this effect: arsenic, ammonium muriate, apiol, strychnine, and other drugs have each been lauded by various observers and evidently on good ground, if, as we believe, the majority of drugs more or less actively stimulate the adrenal system.

Among the agents recommended for the same purpose, *i.e.*, as a febrifuge, is carbolic acid. Trenlich,[97] Declat,[98] and Ringer,[99] among others, having recognized its value as a prophylactic. Though it is not to be recommended as such against malaria, this agent is nevertheless shown by this feature of its physiological action to also produce engorgement of the peripheral capillaries owing to its effect upon the adrenal system.

Packard and Willson,[100] to whose article we have already referred, speak of the treatment of tetanus in the following terms: "Baccelli states that of 40 cases of tetanus treated with carbolic acid subcutaneously only 1 died; and Pinna notes statistics, compiled by Ascoli, of 99 cases treated by Baccelli's method with only 1 death." While they correctly state that no such results are reached in other countries, the fact remains that results vouched for by an investigator of the rank of Baccelli command confidence. It suggests that we should look elsewhere for the untoward results obtained in other countries. That the simultaneous or previous administration of cannabis Indica, chloral, the bromides, etc., commonly used in tetanus, and which, in the light of our views, react upon the adrenal system much as does the tetanus toxin itself, account for these untoward results seems to us very clear. Indeed, the use of such remedies *besides* Baccelli's carbolic-acid treatment can have but one result: *i.e.*, adrenal insufficiency. If, on the other

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[97] Trenlich: Medical Age, vol. 1892.
[98] Déclat: Gazette Hebdomadaire vol. xxvi, 1889.
[99] Ringer: "Hand-book of Therapeutics," 1897.
[100] Packard and Willson: *Loc. cit.*, p. 1020.

hand, Baccelli's method is *alone* resorted to, and the drug be administered in doses *no larger* than those he recommends, we feel confident, if our views are sound, that the results obtained in *all* countries will but coincide with his own. Suffering may require the use of morphine; fortunately, this agent also stimulates the adrenal system, when given in therapeutic doses.

But Baccelli's clinical experience with tetanus when coupled with our views seems to us to suggest a far-reaching application of such energetic adrenal stimulation. Indeed, we have fully emphasized throughout this work the kinship between all conditions attended with convulsions. The main disorders which may be classed as such are: *epilepsy* (other than purely traumatic), *puerperal* and *infantile convulsions*, and *hydrophobia*. Though the latter disease is the only one of the three which presents a direct analogy to tetanus as regards primary cause, *i.e.*, an exogenous virus, the convulsion-producing factor is nevertheless the same in all: *i.e.*, an accumulation in the blood-stream of toxic waste-products incident upon adrenal insufficiency. It follows, therefore, that a treatment similar to that which Baccelli employs in tetanus should also prove effective in all these affections, since it becomes evident that carbolic acid is able not only to counteract the insufficiency of the adrenal system, and cause the latter to resume its normal functional activity, but also to raise this activity *beyond* the normal, flood the circulation with its defensive and offensive weapons, and convert the enemies of the organism into benign elements.

Arsenic is another agent that has been found of great value in malaria. Boudin,[101] one of the pioneers in its use as a prophylactic agency, introduces a suggestive remark which acquires considerable weight when the fact that his experience was acquired while surgeon-general of the French armies in the field during the Algerian campaigns: "I am assured by successive trials, which have been repeated with similar results by many others, that arsenous acid preserves, in the somewhat microscopical doses of $^1/_{100}$ grain, all its medicinal energy, not only in marsh-fevers, but also in a *multitude of other diseases*. Further, I have obtained from $^1/_{100}$ grain of this remedy the

[101] Boudin: "Traité des Fièvres Intermittentes," Paris, 1842.

entire removal of fevers contracted in Algeria and Sénégal and which had previously resisted means of various kinds, including quinine and change of climate." Indeed, when we consider the large number of diseases in which arsenic is now recommended, Boudin's reference to a "multitude" of diseases finds its verification. As a prophylactic its value has been extolled by C. F. Bryan in various affections, including scarlatina.

Directly connected with our views is the fact that arsenic, so extensively employed in skin diseases, is, as stated by Shoemaker,[102] "valuable in proportion to the absence of irritation or acute inflammation." It is obvious that a peripheral inflammatory process, in the light of our views, means the presence of the protective elements—indeed, an excessive proportion of them—in the cutaneous tissues. In the so-called chronic processes, on the contrary, some of which recall, by the dryness of the skin, the same condition in myxœdema, cretinism, etc., the main pathogenic features are the absence of these protective elements and the lowered nutrition which this normally involves. Hence the value of arsenic in cutaneous diseases in which desquamation, dryness, etc., prevail: *i.e.*, psoriasis, the dry form of eczema, impetigo, etc. The connection of the curative process with the adrenal system is well shown by the results obtained by Byrom Bramwell[103] in psoriasis with thyroid extract. Arsenic, as observed by Gautier (see page 156), seems to be a normal constituent of various structures, and, we have seen, is able to counteract the untoward effects of iodine. If the experience of Boudin, Bryan, and others, which illustrates the value of arsenic in a large number of diseases, is added to that of dermatologists as regards the pre-eminent value of this remedy in cutaneous diseases in which nutrition of the skin is impaired,—the whole being traceable, as shown by Bramwell's cases, to the adrenal system,—the far-reaching value of arsenic as an immunizing agent seems self-evident.

Of considerable interest in this connection is the stress laid by C. R. Illingworth[104] upon the use of the biniodide of

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[102] Shoemaker: "Materia Medica and Therapeutics," fifth edition, 1901.

[103] Byrom Bramwell: "Atlas of Clinical Medicine," Plate LXI.

[104] C. R. Illingworth: "The Abortive Treatment of Specific Febrile Disorders by the Biniodide of Mercury," London, 1888.

mercury with the view to aborting scarlatina, diphtheria, measles, variola, varicella, pertussis, parotitis, typhoid fever, typhus, dengue, relapsing fever, pyæmia, puerperal fever, syphilis, leprosy, the plague, hydrophobia, and yellow fever. In keeping with some of the views that prevailed at the time, the author ascribes infectious processes "to the exhausting depredations of the germs more rapidly and extensively exerted than ordinarily upon the oxygen of the corpuscles of the blood"; he also considers the salt as "germicidal and hæmatinic." While this interpretation of the nature of the morbid and curative processes is not in accord with our own, the fact remains that Illingworth is sustained by our views as regards the legitimacy of his results. In other words, while he witnessed the results, we show that such results *can* be reached, and *how* they are reached. Indeed, we will see in another volume that the biniodide of mercury occupies a high position among the stimulants of the adrenal system, owing mainly to its haloid constituent. The feature that we wish to emphasize by referring to Illingworth's observations is the efficacy of stimulation of the adrenal system in arresting incipient morbid processes.

"Abortive treatment" is a familiar expression, and its applicability is not only exemplified by the experience of the few authors we have named, but by that of a multitude of them. The multiplicity of ailments in which a single drug may be used attests to this. It is, therefore, entitled to a prominent position in therapeutics, precisely as is, it seems to us, "immunizing treatment," an expression which seems to us applicable to the scientific use of remedies for the purpose of preventing disease.

Sera, we have seen, are at best only able to supply two constituents, *i.e.*, the trypsin and fibrinogen, while appropriate remedies, by enhancing the functions of the adrenal system, awaken all the resources of the organism to inordinate activity.

Indeed, in the light of our views, nothing in our pharmacopœia approaches antitoxin in value in the treatment of diphtheria, simply because it supplies exactly the missing plasmatic constituent: *i.e.*, trypsin. It is probable that the use of fresh horse-serum will not be found inferior in the treatment of typhoid fever to antitoxin in that of diphtheria, simply because

it supplies precisely the plasmatic constituent required in that disease: *i.e.*, fibrinogen. In all other diseases, however, apart from the unquestionable usefulness of fresh serum in all disorders of an adynamic type to temporarily compensate for some component of the blood-stream that is morbidly reduced quantitatively, the use of drugs seems to us far preferable, while essentially susceptible to scientific application. The history of serum-therapy fully sustains, we believe, our statement regarding the value of sera, but the aggregate of facts we will submit in another volume seems to us to demonstrate that our confidence in the therapeutic value of drugs is not misplaced.

If our views prove sound, we must frankly express our belief that they will enable us, as physicians, to master the greatest scourges of humanity. Indeed, the comparative list on the opposite page will show that *Asiatic cholera* is in reality but the gravest form of adrenal insufficiency, and that many familiar morbid conditions are its prototypes, notwithstanding the variety of causative factors.

Besides hygienic means, the prevention and arrest of the choleraic process and all the kindred disorders mentioned resolve themselves into these few words: *stimulate the adrenal system.* But in doing this it is necessary to remember that large doses cause insufficiency, while the average *therapeutic* dose causes stimulation. We have not been able to master cholera Asiatica because no agent has been used that was capable of sufficiently stimulating the adrenal system. East Indian empirics have found by experience, however, that snake-venom could cure cholera. We have seen how rapidly venom can overwhelm the adrenal system; that we have, among our alkaloids, fully as potent agencies is probable. Trial alone, however, can show which of these can raise the adrenal system from the depths into which the cholera toxins—an aggregate of them—have plunged it, precisely as Baccelli's carbolic-acid treatment succeeds in doing in tetanus.

Pulmonary tuberculosis is another formidable enemy of mankind which, in the light of our views, seems subject to a different interpretation as regards intrinsic pathogenesis. The vulnerability of the system to the bacillus of this disease is readily accounted for if, as we believe, the adrenal system,

either through inherited or acquired insufficiency, is unable to adequately maintain general nutrition. It is not in the lungs, therefore, that the primary endogenous cause of the disease must be sought, but in the adrenal system. Nor is it even in

Symptoms that follow: (1) removal of both adrenals in mammals; (2) hæmorrhage into both adrenals; (3) sudden cessation of adrenal functions as a result of organic disease.	Cardinal symptoms of ASIATIC CHOLERA.	Cardinal symptoms of cholera infantum, cholera nostras; tartar emetic and arsenic acute poisoning; poisoning due to ingestion of certain toxic foods: meat, milk, fish, and mushrooms (phalline) especially.
1. Great weakness, with gradual loss of muscular power.	1. Marked muscular weakness.	1. Rapid loss of strength.
2. Violent abdominal pain.	2. Violent griping pain.	2. Abdominal discomfort and pain.
3. Great reduction of vascular pressure; pulse small and weak.	3. Pulse rapid and weak; sometimes intermittent.	3. Pulse rapid, weak, and intermittent.
4. Temperature subnormal just before death especially.	4. Temperature in mouth and on surface very low, but 104° F. in rectum.	4. Temperature subnormal, but rectal temperature 103° to 105° F.
5. Respiration frequent and difficult; dyspnœa; sometimes cyanosis.	5. Respiration frequent and difficult, and cyanosis.	5. Rapid; labored; Cheyne-Stokes type sometimes.
6. Urine scanty.	6. Urine scanty; sometimes suppressed.	6. Urine scanty; sometimes complete anuria.
7. Abundant liquid stools.	7. Rice-water; serous stools.	7. At first bile-stained stools, and then nothing but serum.
8. Death; coma; convulsions.	8. Coma; convulsions.	8. Coma; convulsions.
9. Proves fatal in from 20 minutes to 3 days.	9. Proves fatal in from 2 to 3 days.	9. Proves fatal in from a few hours to 4 days.

the lungs that we must seek the explanation of the lesions in them, for the element of specificity of the bacillus of tuberculosis does not, as is well known, include limitations to any particular organ.

We have seen how dependent upon the adrenal functions are those of the heart. Even if the nutrient cells, the neutrophiles, and the hæmoglobin cells, the eosinophiles, were supplied in sufficient numbers (leucocytogenesis being inadequate when adrenal insufficiency exists), what would it avail with a weak heart to send them through their distributing channels? Indeed, what there is produced of adrenal secretion, life's pabulum, we may say, cannot even pass the alveoli with *sufficient speed* to adequately supply not only the system at large, but the pulmonary tissues themselves with oxygen. Indeed, we have seen that the activity of *function* in any organ was commensurate with the *speed* with which the oxidizing substance *passed through* that organ. That this also applies to the lungs is strikingly illustrated by the beneficial effects of high altitudes, which, by enforcing a marked increase of cardiac activity, proportionally enhance general nutrition, not only of the lungs, but also that of the adrenal system itself.

But the predominating feature of the morbid process as regards systemic vulnerability to the disease is that connected with the protective functions in the alveoli. Since our study of the subject in the eleventh chapter was submitted, we ascertained that all three varieties of adult leucocytes are present in this most exposed portion of the organism, and that they all contain trypsin. As this substance is ejected with their granules, the eosinophiles, in undergoing conversion into nucleated epithelium, doubtless eliminate theirs along with their large hæmoglobin granules. The cavity of the lobule and the underlying serum must therefore be constantly supplied with this bactericidal and antitoxic fluid (besides the phagocytic neutrophiles), when *the adrenal system is functionally normal.*

Absolute integrity of the adrenal system thus asserts itself as a *sine qua non* of perfect immunity against pulmonary tuberculosis, *i.e.*, against the intrusion of pathogenic germs of any kind (and particularly the tubercle bacillus) in the *circulations*, not only of the lungs, but also of the intestines. We say "circulations," because the lymph is at least as greatly exposed to invasion as is the blood, and is a far better medium for the rapid pullulation of bacteria. Insufficiency of the adrenal system, whether inherited or acquired, when sufficiently advanced

to cause hypoleucocytosis, correspondingly weakens the functional energy of the heart, and two cardinal factors thus unite in rendering the lungs vulnerable to pathogenic elements. As soon as the tubercle bacillus is admitted, it becomes an additional source of adrenal insufficiency, owing to the toxins it generates, and which react upon the anterior pituitary body precisely as would any other equally virulent poison.

All these features bear with equal force upon the intestinal infection by this pathogenic micro-organism, for we must not overlook the fact that trypsin is also secreted into the intestine by the pancreas. If our views are sound, therefore, Koch is not sustained when he says that human beings are not susceptible to bovine tuberculosis; still, this is only true when the intestinal protective functions, including the production of trypsin, are impaired through adrenal insufficiency. On the other hand, his views *are* sustained when perfectly protected human beings, *i.e.*, subjects possessed of an adrenal system in full functional activity, form the basis of his deductions.

The value of immunizing medication seems to us to cover a vast field of usefulness in this connection. The family history, and many other features considered as etiological factors of tuberculosis, afford landmarks for the adoption of preventive medication long before the morbid process has had time to develop,—long, indeed, before infection can have occurred. During adolescence, for example, particularly when the family history is unfavorable, medication calculated to raise or develop the functional activity of the adrenal system to a high standard, must, in the light of the views submitted, not only prevent the development of pulmonary or any other form of tuberculosis, but arrest it in its earlier stages.

Pneumonia, the mortality of which remains the same notwithstanding the material improvement in that of phthisis, does not present the characteristics of disease susceptible to prevention. Indeed, lobar pneumonia, for instance, seems to us to exemplify a process wherein death occurs owing to excessive functional activity of the adrenal system. This is shown especially by the hyperleucocytosis, the high fever, the flushed face, the high temperature, the bounding pulse, etc. The conception is furthermore sustained by the remarkable results (a 2.64-per-

cent. mortality) reported by Petresco[105] with very large doses of infusion of digitalis, and by a large number of clinicians with veratrum viride, but only when used during the sthenic stage. In the light of our views these agents, which normally bring on adrenal insufficiency, lower the excessive adrenal activity of pneumonia sufficiently to prevent the dangerous engorgement of the first stage, and, therefore, that of gray hepatization and its main consequence: the asthenic stage. In the latter, of course, the adrenal system must be supported, but with due care, owing to the increased likelihood of adrenal insufficiency.

Insanity, when due to factors other than structural changes, seems to us to present many phases that are directly traceable to insufficiency or overactivity of the adrenal system. The splendid studies of Andriezen and Berkley have enabled us to show the morbid effects of adrenal overactivity as caused by alcohol, ricin, etc., upon the neurons and the structures that supply them with their plasma: *i.e.*, with oxidizing substance. Since then, we have seen that leucocytosis also means an excessive supply of the primary source of energy: *i.e.*, of myelin granules. We therefore have, as a result of the excessive use of any agent capable of exciting the adrenal system, not only the mechanical dilation or beading of the dendrites shown in the plates we have reproduced, but excessive metabolism within the neurons. That exaltation, the various forms of mania, etc., should develop under such conditions, particularly in individuals predisposed to mental disorders through inherited cerebral malnutrition, is self-evident. On the other hand, a similar predisposition, or continued cerebral malnutrition incident upon a debilitated adrenal system, can normally become a cause of the various forms of melancholia, dementia, idiocy, etc. We have traced cretinism to adrenal insufficiency, and have adduced evidence tending to prove that absence of the thymus—the main active factor of which is phosphorus—coincided with idiocy in a large proportion of cases. What have we here but impaired nutrition of the cerebral structures through insufficiency of their main dynamic elements: phosphorus and oxygen?

Immunizing medication here can obviously render great

[105] T. G. Ashton: "Sajous's Analytical Cyclopædia of Practical Medicine," vol. v.

service, but only when the pathogenesis of each form is thoroughly established. Some cases of acute mania, for instance, may require stimulation of the adrenal system, simply because the engorgement of the neurons may find its cause, not in an exogenous poison, but in accumulation of physiological toxics, which, as is the case in epilepsy, tetanus, etc., give rise to sudden exacerbations of adrenal activity: *i.e.*, to explosions of functional activity calculated to rid the organism of the morbific agencies by a process of active combustion.

Another feature which must not be overlooked in mental disorders is the influence exerted upon them of fluctuations in the functional activity of the posterior pituitary body. As the *sensorium commune*, it necessarily takes part in all emotional states. Indeed, hysteria appears to us to be essentially a disorder of the posterior pituitary body. This organ, as may readily be surmised, is likewise the seat of perturbations attended by a distinct line of symptoms. Influenza, hay fever, neurasthenia, neuralgia, and several other obscure neuroses are all, in fact, syndromes in which the posterior pituitary body plays a leading part. In diseases of the heart, vascular system, digestive apparatus and skin, this organ necessarily takes part in the production of the phenomena witnessed, owing to its identity as the general center of vagus.

Syphilis.—Although the influence of the posterior pituitary body in all these processes has necessitated a special line of analysis that will be submitted in another volume, we may here refer to the fact that simultaneous impairment of the functions of both the anterior and posterior pituitary bodies accounts for the ravages of syphilis. Indeed, we have seen that these two organs are the governing centers of all vital processes; it is these, therefore, that this fell disease undermines. That such is the case is not only suggested by the inquiry to which we refer; it is also revealed by the character of the agency which best overcomes its more advanced stages: *i.e.*, the medicinal prototype of Nature's own adrenal stimulant: iodine,—but so combined with a normal constituent of the blood-stream, potassium or sodium, as to further assist the *vis medicatrix naturæ* itself.

Indeed, if our views are sound, the adrenal system is the

physician of the organism—one whose beneficient mission we can govern at will by the many valuable agencies which science has placed in our hands.

ALKALINITY OF THE BLOOD AND THE PRESERVATION OF LIFE DURING DISEASE.

We began this chapter with an allusion to the remarkable life-saving value of saline solution. As is well known, the alkaline reaction of the blood is exceedingly marked, and is mainly due to the sodium salts the serum contains. Charrin[106] gives this reaction the first place among the protective properties of the blood and body-fluids, and rightly deems it an essential condition of normal life. When it is reduced through alimentation, abnormal fermentation, the virulence of various micro-organisms, and deviations from the normal chemical reactions of which the body-fluids, etc., are the seat, correspondingly marked disturbances in the blood occur, with disease as a result.

Furthermore, the globulins, which normally contain 6 per cent. of potassium salts and $^{6}/_{10}$ of 1 per cent. of sodium salts, and the albumoses are kept in solution in the plasma by these salts. Chloride of sodium, besides this rôle, facilitates osmosis and diapedesis. When it is recalled that several grammes of this salt pass out of the organism in the urine daily, probably assisting in the excretion of waste-products, besides the two grammes which are eliminated with sweat, its rôle in the preservation of conditions favorable to the maintenance of tissue-metabolism becomes evident. The di-sodium phosphates, found in all tissues and fluids, usually in association with the sodium carbonates, are active in insuring the alkalinity of the plasma, the lymph, the pericardial fluid, the cephalo-rachidian fluid, the mucus (excepting the vaginal), the tears, the milk, the synovia, the spermatic juice, the aqueous humor, the saliva, the bile, the pancreatic juice, and the large intestine. The sulphates of sodium and potassium are also found in the majority of the above fluids, along with other salts in smaller proportions. This alkalinity is of great indirect importance in another direction: *i.e.*, it enables the blood to

[106] Charrin: "Les Défenses Naturelles de l'Organisme," 1898.

carry an adequate quantity of CO_2, and thus assists it in efficaciously ridding the organism of this gas.

The classical teachings in respect to the importance of the blood's alkaline reaction in all vital functions are not only sustained by our labors, but greatly emphasized in view of the manner in which the various leucocytes we have studied distribute their granules of peptone, myosinogen, fibrinogen, hæmoglobin, and myelin. Any modification in the fluidity and constituents of the plasma must necessarily compromise this all-important function, and, if we recall the fact that chloride of sodium takes part in the intranuclear reaction of all leucocytes, it will become apparent that the presence of this salt in adequate proportion in the plasma is as paramount to the continuation of life's processes as is oxygen itself. Even trypsin will not act in the absence of salts. Metchnikoff, we have seen, found that trypsin was the active body of the intraphagocytic alexin; referring to the latter, he writes[107]: "It only acts in the presence of salts. When relieved of its salts by dialysis, the serum loses its hæmolytic power, but, as soon as these salts are restored to it, this power reappears."

The remarkable results obtained by the *timely* administration of saline solution either subcutaneously, intravenously, or by way of the rectum in febrile diseases, uræmia, puerperal eclampsia and other infections, hæmorrhage, etc., and which in some cases have restored sufferers deemed to be *in extremis*, are thus accounted for. Indeed, some of the instances reported could almost be considered as resuscitations.

Experimental bacteriology forcibly shows the importance of the alkaline reaction of the blood-fluids as a protective factor. The experiments of Behring and Nissen[108] led them to conclude that the resistance of the white rat to anthrax was due to the intense alkalinity of its blood; Paul[109] not only supported this view, but also found that, if the alkalinity of rabbit's serum was neutralized, its germicidal powers disappeared.[110] These observations were further sustained by von

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[107] Metchnikoff: *Loc. cit.*, p. 93.
[108] Behring and Nissen: Zeitschrift für Hygiene, Bd. vii, 1890.
[109] Paul: "Proceedings of the Royal Society," London, May 22, 1890.
[110] McFarland: "Pathogenic Bacteria"; edition, 1900.

Fodor,[111] who ascertained that this resistance to anthrax could actually be increased in rabbits by the injection of an alkaline solution, and by Blumenthal,[112] who experimentally found that the formation of bactericidal products in the circulation depended upon the degree of the blood's alkalinity. Calabrese, of Naples,[113] also conducted a series of valuable experiments in this connection. He immunized animals with attenuated, virulent cultures of bacterial toxins at different times, and determined the degree of alkalinity in each instance by an accurate dosimetric method. He invariably found the alkalinity of the blood to increase with the degree of immunization, and the alkaline reaction only attained its maximum when the animal had become totally refractory. The blood reacted toward the toxic agent by a very gradual, though persistent, increase of the alkalinity. Healthy, non-immunized animals, on the other hand, first showed a more or less sudden evidence of alkalinity, but this declined, and the fall became marked during the few hours preceding death.

In the face of such evidence, to which much more could be added, we can certainly ascribe to the alkaline salts of the blood a most important part in the protective process. But how do they exercise their function? Evidently not as neutralizing factors, as already stated, but in virtue of an action directly exercised upon the fluids or cellular elements. And "cellular elements" mean more than the generally accepted sense given these words, if our views are sound, for they include the leucocytes and erythrocytes, the general center of the protective system itself, the anterior pituitary, and its co-center in preserving vital functions: the posterior pituitary body.

Indeed, the adrenal system asserts itself in a new capacity in this connection, for experimental evidence suggests that, in addition to its other functions, it also governs the alkalinity of the blood. Thus, von Fodor also found that, when rabbits were infected with anthrax, typhoid, cholera, tuberculosis, and erysipelas toxins, the alkalinity of their blood *rose*, but *declined* as the effects of the disease became more marked. Cantani

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[111] Von Fodor: Centralbl. für Bakt. u. Parasit., vol. vii, 1890.
[112] Blumenthal: Zeitschrift für klin. Med., Bd. xxviii, 1895.
[113] Calabrese: La Semaine Médicale, Oct. 30, 1895.

observed the same phenomenon under the use of diphtheria toxins. The influence of the adrenal system also becomes evident through the facts (1) that the increase of alkalinity only showed itself *two hours* after the poison had been injected; and (2) that it slowly increased until the twentieth hour had been reached, then gradually fell, returning to the normal when a period of three days had elapsed. In another series of experiments, performed with the collaboration of Rigler,[114] von Fodor adduced suggestive evidence. In this series he observed that the intensity of the symptoms varied with the dose of toxin injected: moderate doses increasing the alkalinity, while very large doses caused it to decrease. Again, an important clinical feature: while the injection of diphtheria toxin lowered the alkalinity of the blood, *injections of antitoxin raised it.* Finally, we have shown how clearly leucocytogenesis was dependent upon overactivity of the adrenal system: Löwy and Richter,[115] in a series of experiments with hemialbumose, spermin, peptone, and antitoxin in rabbits, noted that the increase of white cells kept pace with that of alkalinity. It therefore seems clear to us that:—

1. Both leucocytosis and increased alkalinity of the blood are concomitant results of the enhanced functional activity of the adrenal system induced by toxics.

2. It is only when the alkalinity and fluidity of the blood-plasma are approximately normal that all cellular elements of the organism, including the adrenal system and the posterior pituitary body, can continue their functions.

The lethal tendency engendered by a deficiency of salines in the blood during disease is not only due to the fact that cellular metabolism is inhibited through the increased density of fluids and cells, but there is another factor which contributes materially to augment the morbid results of such a condition: *i.e.*, the primary prophylactic process itself. Indeed, in virtue of the principle we now have so frequently emphasized, the various poisons, toxins, toxalbumins, etc., awaken a defensive reaction in the organism by primarily stimulating the adrenal system. But in doing this it augments to an inordinate degree

[114] Rigler: Centralbl. für Bakter., Feb. 6, 1897.

[115] Löwy and Richter: Deutsche med. Wochenschrift, No. 33, 1897.

the combustion processes and simultaneously the physiological consumption of the salts.

If we now seek for a compensative supply, it soon becomes evident that none is available.

During health the sodium chloride needed by the organism is ingested with the food, both as a condiment and as a constituent of meats, vegetables, etc.; the alkaline phosphates and the sulphates likewise form part of our diet, the latter salts being also obtained from most drinking-waters. As to the alkaline carbonates, they are products of dissociation of acids ingested with vegetables and fruits. All the alkaline salts referred to are thus ingested with foods or beverages. During disease, on the other hand, anorexia, the restricted or modified diet, etc., involve, if anything, a marked reduction in the amount of alkaline salts ingested. It thus becomes evident that a morbid cycle exists, in this connection, pernicious in the extreme to the welfare of the patient in febrile disorders, because, the source of these salts being *external to the organism*, the latter is possessed of no intrinsic reserve. *Steadily, as the febrile process advances, the alkaline salts are consumed, and, being inadequately renewed, the vital and defensive functions are increasingly hampered until life ceases.*

There is still another phase of the morbid process which further increases the lethal tendency: *i.e.*, the fact that, while the alkaline salts are being reduced through the foregoing factors, the increased prophylactic activity of the adrenals correspondingly augments the vigor of tissue-metabolism and causes accumulation of waste-products. We thus have a new source of intoxication added to that incident upon the disease itself.

Besides the aggravation of all symptoms which this engenders,—a source of considerable confusion in diagnosis,—this complication easily accounts for a perplexing experimental result reported by Charrin and Langlois to which we have already referred: *i.e.*, the fact that an animal from which one adrenal has been removed lives longer after pyocyaneous culture infection than a normal animal poisoned in the same way. Oppenheim[116] more recently confirmed this observation with diph-

[116] Oppenheim: Comptes-rendus de la Société de Biologie, March 16, 1901.

theria toxins. It seems to us that the animals deprived of one adrenal were correspondingly less exposed to excessive tissue-waste under the stimulating influence of a toxin than those possessed of both their organs. Through the excessive metabolism at first induced in the latter, soon followed by adrenal insufficiency and inhibition of all oxidation processes, toxic waste-products were added to the toxin, thus submitting the normal animals to the effects of two poisons, while the mutilated ones suffered from those of only one.

If this factor is added to those previously described, the *absence of plasmatic salts* not only hampers the vital and defensive functions of the organism, but it soon *becomes an indirect source of general toxæmia which insures a fatal result even in relatively benign cases.*

A disease in which the mortality has remained practically unabated, notwithstanding the quantity of faithful work devoted to the elucidation of its pathology and treatment, is pneumonia. This seems to us accounted for mainly by the fact that the functional dependence of leucocytes upon the chlorides has been entirely overlooked. Metchnikoff states, we have seen, that trypsin only acts in the presence of salts, and that serum loses its hæmolytic power when relieved of them; again, we have referred to the experiments of Kossel, which suggest that alkaline salts are factors in the intranuclear reactions. The relatively enormous excess of leucocytes which invade the lungs during the primary stage of this disease necessarily involves the use of a correspondingly great quantity of these salts, the nucleus and the trypsin soon appropriating all those available. How are these salts replaced? The answer readily appears in the light of the foregoing deduction: In a large proportion of cases they are not replaced, and death occurs.

Frederick P. Henry, of Philadelphia, who was the first clinician to resort to this measure (1889), says[117]: "The surest method of conveying water to the tissues is by subcutaneous injections of (deci-) normal saline solution: a solution of common salt of the strength of 50 grains to a pint. About three years ago a number of cases of pneumonia at the Philadelphia

[117] Frederick P. Henry: Hare's "System of Practical Therapeutics," first edition, vol. ii, p. 290, 1892.

Hospital were treated by the writer in this manner and with excellent results, both as regards palliation and cure."[118] This method was also used by him in the worst types of lobar pneumonia met with: *i.e.*, those that occur in drunkards, alcoholic intoxication, exposure and a debilitated adrenal system incident to the alcohol habit, concurring to place the patient on the brink of death almost from the start. After vividly describing a case of this kind he remarks: "Such cases treated by ordinary methods terminate, as a rule, with few exceptions, in death. Such cases treated by hypodermoclysis terminate, as a rule, in recovery." In the light of our investigations, the immediate use of this measure, *i.e.*, as soon as the diagnosis is established, becomes imperative, and the fact that even during health about $^1/_2$ ounce of chloride of sodium alone is voided with the excretions in twenty-four hours (Purdy), points to the need of its frequent introduction into the organism during disease.

Again, it seems to us that the mortality of diphtheria could still be further reduced were the saline solution considered as a necessary accompaniment of antitoxin injections. In all the diseases to which we have referred in the foregoing pages, tetanus, typhoid fever, scarlatina, and small-pox especially, a reduction of alkaline salts in the blood-stream can likewise, it seems to us, be distinctly discerned; and, if our interpretation of the scheme of life is not erroneous, most of them owe their lethal tendency mainly to this cause. Even apart from the more exact solutions employed, mere rectal injections of a solution composed of chloride of sodium, one drachm to the pint of water, at 104° F. (40° C.), renewed once in awhile have often kept death at bay and insured recovery. Why not supply the system from the outset of a febrile disease, or, indeed, any other general disorder, with the constituents that preserve the mechanical freedom of all nutritional and protective functions, including those of the adrenal system itself? The colon is also provided with solitary lymph-follicles which supply leucocytes capable of appropriating from the intestinal contents all useful constituents. The presence of such a fluid in the colon, judging from the promptness with which some patients revive when it is used, evidently gives rise to marked activity in this

[118] Editorial, Medical News, July 6, 1901.

region, for the process requires rapid production of leucocytes, followed by absorption of the injected fluid by the cells and immediate return of the latter to the blood-stream to distribute their charge throughout the entire organism. In the so-called "diathetic" diseases, including rheumatism, gout, and migraine, the use of saline solution enemata, and, if need be, hypodermoclysis, or of saline waters by the mouth, should prove beneficial in addition to the remedies administered. Indeed, the reputation acquired by many of the best-known watering-resorts in Europe is admittedly due, as is well known, to the alkaline salts which the patients ingest in large quantities and to the well-regulated *régime* prescribed for them by the local physicians. In the treatment of tuberculosis it constitutes an essential measure.

Certain growths, particularly the more malignant forms, sarcoma and carcinoma, seem closely connected with adrenal insufficiency and its normal consequences. We have seen that trypsin, fibrinogen, and the oxidizing substance were simultaneously necessary to insure the destruction of cells even *in vitro*, and, furthermore, that this process required, in addition, the presence of alkaline salts. That the destruction of worn-out or degenerated cells is a function of these very elements in the blood is evident. Insufficiency of the adrenals, therefore, by reducing the relative proportion of these four constituents in the blood-stream must correspondingly inhibit this physiological process in all parts of the organism.

As to sarcoma, the similarity between the cellular elements of the small round-celled variety and mononuclear leucocytes is striking; each cell shows its nucleus, fibrils, and granules, though, of course, more or less modified, owing to the abnormal environment. The large round-cell sarcoma recalls the metamorphosis into epithelial cells which eosinophiles undergo in the pulmonary alveoli; indeed, the cells of melanosarcoma contain the blood-pigments themselves. Grouped as sarcomata are now, according to the variety of connective tissue which forms their frame-work, we have, as is well known, myo-, lympho-, fibro-, myxo-, glio-, osteo-, chondro-, myelo-, melano-, angio-, and finally neuro- sarcoma, all of which clearly indicate that any part of the system in which nutrition is, from one cause

or another, relatively impaired, may become the seat of this malignant growth, or rather of a *local accumulation* of the aberrant or worn-out cells which enter into its formation. The great vascularity of these growths suggests an effort of Nature to cause their elimination, but mitotic proliferation is alone induced, the blood being deficient in the four constituents which should insure destruction of the morbid cellular elements.

Apart from the marked vascularization peculiar to sarcoma, the same pathological process obtains, it seems to us, in cancer, although here we are dealing with a localized accumulation, retention, and proliferation of epithelial cells. Their multiplication *in situ* occurs (as in sarcoma) partly in virtue of the fact that they "cannot fully utilize the assimilated material in the performance of [their] specific functions" (Adami[119]) and partly because the potential energy of their nuclei becomes converted into sufficient heat-energy (with what oxidizing substance reaches them) to induce proliferative activity. Ritter[120] found the nuclear chromatin to be precisely that of normal tissue and the cellular karyokinesis to differ in no way from that observed in the normal physiological process.

Adrenal insufficiency also accounts for the complications witnessed. As the accumulated elements degenerate, toxic products of decomposition enter the blood and, by lowering the functional activity of the anterior pituitary body, finally bring on the cachectic stage. The foci of retained cellular elements becomes also more numerous: *i.e.*, "metastasis" occurs in one or more regions. That the adrenal system is primarily at fault is also suggested by the predilection of the aged to malignant growths, the recognized influence of "general debility," localized malnutrition as a result of trauma, cicatrices, etc., and by the fact that the only internal remedies that have proven of any value whatever are powerful adrenal stimulants: erysipelas toxins (Fehleisen), erysipelas and bacillus prodigiosus toxins (Coley), thyroid extract (Dorland), lysol and iodine (Behle-Luckau), sodium cacodylate (Benoit), and the better known arsenic, quinine, etc.

Owing to the adrenal stimulation induced, the four con-

[119] J. George Adami: British Medical Journal, March 16, 1901.
[120] Ritter: Deutsche med. Wochenschrift, June, 1901.

stituents capable of disintegrating the morbid cellular elements, trypsin, fibrinogen, oxidizing substance, and alkaline salts, are supplied to the blood, and these, under normal circumstances, should cause disappearance of the growth. But unfortunately such a result is but rarely reached even under the violent adrenal stimulation which Coley's toxins must cause. How account for this? The Roentgen rays, as suggested by the results already obtained, seem to us to supply one of the missing factors upon which the curative process depends, *i.e.*, a local accumulation of heat-energy and a congestive process through which neutrophile leucocytes (owing to their phagocytic and fibrinogenic properties) are caused to immigrate into the growth in large numbers, to convert the degenerated cellular elements into benign products. Here again, however, the curative process requires alkaline salts in addition to those normally utilized by the organism, in order to insure the full hæmolytic activity of the tryptic intraphagocytic digestion. The frequent use of saline solution thus asserts itself as the remaining measure indicated to insure success in the bloodless treatment of malignant tumors.

In the light of our views, it seems evident that, notwithstanding its simplicity, the use of saline solution represents one of the most valuable measures in the domain of therapeutics, because it defeats the most ubiquitous and efficient morbid influence with which the organism has to contend. On the whole, our analysis of the question seems to us to have shown that:—

1. In all febrile diseases the alkaline salts of the blood and cells are rapidly utilized, and, the organism depending upon the salts ingested with foods for its supply, the anorexia and the reduced diet incident upon the disease tend greatly to aggravate the morbid process.

2. The primary effect of deficiency of alkaline salts in the blood being to inhibit nutrition, impair the efficiency of, and finally arrest, the organism's protective functions, it constitutes one of the most active causes of death.

3. The use of saline solution may be beneficial even in desperate toxæmic cases when the functions of the adrenal system have reached the lowest stage of insufficiency.

4. When a favorable reaction does not follow the use of saline solution, it is because the adrenal system also requires direct stimulation, such as that afforded by strychnine, digitalis, etc., administered subcutaneously.

5. The use of saline solutions is also indicated in general or local chronic diseases due to, or associated with, insufficiency of the adrenal system.

The pre-eminent part we ascribe to salt solution in the preservation of the functional integrity of the cellular elements and of the fluids by which they are surrounded becomes a normal consequence when, as suggested by modern cosmogony and palæontology, sustained by the teachings of comparative anatomy and embryology, the origin of cellular life is traced back to the primitive seas. The many vestigial structures which the human frame exhibits as relics of its evolutional past not only include evidences of a primitive aquatic existence, the embryonic branchial or gill- clefts and the pituitary bodies, for instance; but the plasma in which all the cells of the organism bathe may be said to also typify the original medium, and to assert by its composition, its claim to recognition as a factor of a problem which is destined to revolutionize every department of human thought: *i.e.*, the origin of species. At the Thirteenth International Medical Congress, René Quinton maintained that all aggregates of cells, such as those represented by our organs, were essentially colonies of marine cells, which required as a *sine qua non* of their existence their original environment. Sea-water, he also contended, differs little, if at all, from the blood-plasma in composition. Our own labors confirm this interpretation. Whether immersed in its primordial fluid, as is the elementary marine cell, or traversed by its prototype, the blood-plasma, as are the cellular colonies of which all organs are built, matters little: All find in the saline medium's constituents the agencies necessary to their continued existence. Even the governing center of the adrenal system, the anterior pituitary body, which differs from all other cellular aggregates and the elementary cell itself in that its functional activity is upheld by a special agency, is dependent for the latter upon a constituent of marine plants and sea-water: *i.e.*, iodine.

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